# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Clinical Packet
# November 14, 2012

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# Pharmacy and Therapeutics (P&T) Committee
# Helpful Hints/Reference Document

## P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

## Preferred Drug List/Program Definitions

**Preferred Drug:** Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

**Non Preferred Drug:** Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

**Non Covered Drug:** In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over the counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Benzodiazepines and barbiturates with the exception of those specified by the Alabama Medicaid Agency
- Agents used to promote smoking cessation, unless authorized for pregnant females or plan first recipients
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

**Prior Authorization (PA):** Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are in Non-preferred status or if they required PA prior to the PDL

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

**Override:** Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

**Electronic PA (EPA):** The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

## Prior Authorization Criteria Definitions

- **Appropriate Diagnosis:** Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

**Prior Treatment Trials:** Prior authorization requires that two (2) prescribed generic, OTC or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic, OTC or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic, OTC or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, OTC, or brand.

**Stable Therapy:** Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

**Medical Justification:** An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the

physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

# External Criteria

## Antihistamines (First Generation)

### Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

### Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

### Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

### Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

### PA Approval Timeframes

- Approval may be given for up to 12 months.

### Electronic Prior Authorization (PA)

- Antihistamines are included in the electronic PA program.

### Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

# Estrogens

## Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

## Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred estrogens in this class, either generic, OTC or brand, within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

## Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

## Medical Justification

- Medical justification may include peer reviewed literature, medical record documentation, or other information specifically requested.

## PA Approval Timeframes

- Approval may be given for up to 12 months.

## Electronic Prior Authorization (PA)

- Estrogens are included in the electronic PA program.

## Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

# Antidiabetic Agents

## Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

## Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred antidiabetic agents, either generic, OTC or brand, within the past 12 months, or have a documented allergy or contraindication to all preferred agents in this class.

- If the request is for Avandia®, Avandamet®, or Avandaryl®, the patient must also have failed a 30-day treatment trial with at least two prescribed and preferred antidiabetic agents (of which one is Actos®), either generic, OTC or brand, within the past 6 months.

- If the request is for Symlin®, the patient must also be on insulin therapy and have a hemoglobin A1c greater than 7% despite more than 90 days of insulin therapy.

## Stable Therapy

- Approval may be given for those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

## Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

## PA Approval Timeframes

- Approval may be given for up to 12 months.

## Electronic Prior Authorization (PA)

- Antidiabetic agents, excluding Symlin®, are included in the electronic PA program.

## Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

# Prenatal Vitamins

## Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

## Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

## Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

## Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

## PA Approval Timeframes

- Approval may be given for up to 12 months.

## Electronic Prior Authorization (PA)

- Not Applicable

## Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

**AGENDA**

**ALABAMA MEDICAID AGENCY**
**PHARMACY AND THERAPEUTICS (P&T) COMMITTEE**

**November 14, 2012**
**9:00 a.m. – 12:00 noon**

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1. Opening remarks……...……..Chair
2. Approval of August 8, 2012 P&T Committee Meeting minutes……...…Chair
3. Pharmacy program update…….…...….……...Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews…University of Massachusetts Medical School Clinical Pharmacy Services
   - First Generation Antihistamines
     - Ethanolamine Derivatives-AHFS 040404
     - Ethylenediamine Derivatives-AHFS 040408
     - Propylamine Derivatives-AHFS 040420
   - Estrogens-AHFS 681604
   - Alpha Glucosidase Inhibitors-AHFS 682002
   - Amylinomimetics-AHFS 682003
   - Biguanides-AHFS 682004
   - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors-AHFS 682005
   - Incretin Mimetics-AHFS 682006
   - Insulins-AHFS 682008
   - Meglitinide-AHFS 682016
   - Sulfonylureas-AHFS 682020
   - Thiazolidinediones-AHFS 682028
   - Antidiabetic Agents, Miscellaneous-AHFS 682092
   - Multivitamin Preparations: Prenatal Vitamins-AHFS 882800
6. Results of voting announced……...……...…….Chair
7. New business
8. Next meeting date: February 13, 2013
9. Adjourn

# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of First Generation Antihistamines
# Ethanolamine Derivatives, AHFS Class 040404
# Ethylenediamine Derivatives, AHFS Class 040408
# Propylamine Derivatives, AHFS Class 040420
# November 14, 2012

## I. Overview

The $H_1$-antihistamines are approved for the treatment of allergic and non-allergic conditions; however, they are primarily used for the management of allergic rhinitis, urticaria and angioedema. Allergic rhinitis is a common disorder that is associated with significant morbidity, including lost school/work days, interference with activities of daily living, and a decrease in quality of life. Nasal symptoms include sneezing, itching, rhinorrhea and congestion. Rhinitis may also be accompanied by symptoms involving the eyes, ears and throat.[1] Urticaria is a common disorder characterized by pruritic, raised, erythematous plaques. Lesions may appear on any part of the body; however, they frequently appear on the trunk and extremities. As is seen with allergic rhinitis, intense itching may interfere with sleep, school/work productivity, and quality of life. Angioedema is characterized by swelling of deeper subcutaneous tissues, with less circumscribed lesions. It often involves the face, eyelids, lips and tongue, and may be life-threatening if laryngeal edema or tongue swelling obstructs the airway.[2,3]

$H_1$-antihistamines reduce the physiologic effects elicited by histamine at the $H_1$-receptor; however, they do not prevent the release of histamine or bind to histamine that has already been released. They are classified as first generation and second generation agents. First generation antihistamines bind to both central and peripheral $H_1$-receptors, whereas second generation agents are more selective for peripheral $H_1$-receptors. As a result, the first generation antihistamines may cause sedation, performance impairment in school and driving, as well as anticholinergic effects.[4]

The first generation antihistamines include ethanolamine derivatives (carbinoxamine, clemastine, diphenhydramine and doxylamine), ethylenediamine derivatives (pyrilamine) and propylamine derivatives (brompheniramine, chlorpheniramine, dexchlorpheniramine and triprolidine). They are available as single entity agents, as well as in combination with other first generation antihistamines and oral decongestants.

The first generation antihistamines that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The eye, ear, nose, and throat anti-allergic agents (American Hospital Formulary Service 520200) were previously reviewed and are not included in this review. The majority of the first generation antihistamines are available in a generic formulation and several agents are also available over-the-counter. Cough and cold products are an excludable/optional drug class in accordance with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90). Brand cough and cold products are not covered by Alabama Medicaid; therefore, these products were not included in this review. The second generation antihistamines (acrivastine, cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine) are not included on the mandatory preferred drug list. Brand products currently require prior authorization. Covered generics and over-the-counter products (unless otherwise specified) do not require prior authorization. Although the second generation antihistamines may be mentioned throughout this review, they are not being considered for preferred status at this time. This class was last reviewed in May 2010.

**Table 1. First Generation Antihistamines Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| **Ethanolamine Derivatives** | | | |
| Carbinoxamine | liquid, tablet | Arbinoxa®* | carbinoxamine |
| Clemastine | syrup, tablet | Tavist-1®*‡ | clemastine |
| Diphenhydramine | capsule, chewable tablet, elixir, injection, liquid, syrup, tablet | N/A | diphenhydramine |

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Doxylamine | chewable tablet, tablet | Aldex-AN®‡ | doxylamine |
| Phenylephrine and diphenhydramine | chewable tablet | Aldex CT®‡ | none |
| **Ethylenediamine Derivatives** | | | |
| Phenylephrine and pyrilamine | suspension, tablet | Aldex D®‡*, Poly Hist Forte®‡ | phenylephrine and pyrilamine |
| **Propylamine Derivatives** | | | |
| Brompheniramine | drops | J-Tan PD®‡ | none |
| Chlorpheniramine | extended-release tablet, syrup, tablet | N/A | chlorpheniramine |
| Dexchlorpheniramine | syrup | N/A | dexchlorpheniramine |
| Phenylephrine and brompheniramine | suspension | Vazobid-PD®‡ | none |
| Phenylephrine and chlorpheniramine | drops, liquid, tablet | Cardec®*‡, Dallergy®*‡, Ed Chlorped D®‡, Lohist®‡ | phenylephrine and chlorpheniramine |
| Phenylephrine, pyrilamine, and chlorpheniramine | suspension | Phena-S 12® | none |
| Pseudoephedrine and brompheniramine | drops, liquid | J-Tan D PD®‡ | pseudoephedrine and brompheniramine |
| Pseudoephedrine and chlorpheniramine | drops, liquid, tablet | Neutrahist®*‡ | pseudoephedrine and chlorpheniramine |
| Pseudoephedrine and triprolidine | liquid, syrup, tablet | Ed A-Hist Pse®*‡, Pediatex TD®*‡ | pseudoephedrine and triprolidine |

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
N/A=Not available
PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the first generation antihistamines are summarized in Table 2.

**Table 2. Treatment Guidelines Using the First Generation Antihistamines**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **The Diagnosis and Management of Anaphylaxis: An Updated Practice Parameter[5] (2010)** | Immediate intervention<br>• Aqueous epinephrine 1:1,000 dilution (1 mg/mL), 0.2 to 0.5 mL (0.01 mg/kg in children; maximum, 0.3 mg dosage) intramuscularly or subcutaneously every five minutes, as necessary, to control symptoms and increase blood pressure. No data support the use of epinephrine in anaphylaxis through a non-parenteral route.<br><br>Subsequent emergency care<br>• Consider parenteral diphenhydramine (1 to 2 mg/kg or 25 to 50 mg/dose). $H_1$-antihistamines are considered second-line therapy to epinephrine and should never be administered in lieu of epinephrine in the treatment of anaphylaxis.<br>• Consider parenteral ranitidine (50 mg in adults and 12.5 to 50 mg [1 mg/kg] in children). Parenteral cimetidine (4 mg/kg) may also be used in adults, but no pediatric dosage in anaphylaxis has been established. The combination of diphenhydramine and ranitidine is more efficacious than diphenhydramine alone. These agents should never be used alone in the treatment of anaphylaxis and are considered second-line therapy to epinephrine. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Consider inhaled beta-agonist (e.g., albuterol metered dose inhaler two to six puffs or nebulized, 2.5 to 5 mg in 3 mL saline and repeat as necessary) for the treatment of bronchospasms that are resistant to adequate doses of epinephrine.<br>• Glucocorticosteroids are not acutely effective and should never be used in place of or prior to epinephrine.<br>• When anaphylaxis is not responding to the above measures, including repeated doses of intramuscular or subcutaneous epinephrine, vasopressors and glucagon may be considered. |
| American Academy of Dermatology (AAD) Clinical Guidelines Task Force: **Guidelines of Care for Atopic Dermatitis[6] (2004)** | Topical agents<br>• Topical corticosteroids are the standard of care for the treatment of atopic dermatitis.<br>• Emollients are a standard of care, steroid-sparing, and useful for prevention and maintenance therapy.<br>• Pimecrolimus and tacrolimus have been shown to reduce the extent, severity, and symptoms of atopic dermatitis in adults and children.<br>• Tar may be associated with therapeutic benefits, but is limited by compliance.<br>• Short-term adjunctive use of topical doxepin may reduce pruritus, but adverse events may limit its usefulness.<br><br>Antibiotics and antiseptics<br>• Patients with atopic dermatitis are commonly colonized with *Staphylococcus aureus*. Systemic and topical antibiotics temporarily reduce *S aureus* colonization on the skin.<br>• Oral antibiotics have a minimal therapeutic effect on the dermatitis without signs of infection. Oral antibiotics can be beneficial when skin infection is present.<br>• Topical antibiotics can be effective when infection is present; however, development of resistance is a concern.<br><br>Oral antihistamines<br>• There is little evidence that sedating or nonsedating antihistamines are effective in relieving itch or urticarial symptoms associated with atopic dermatitis.<br>• For patients with significant sleep disruption due to itch, allergic dermatographism, or allergic rhinoconjunctivitis, sedating antihistamines may be useful.<br>• Many patients with atopic dermatitis may also have allergic rhinoconjunctivitis, urticaria, and dermatographism and may benefit from the use of antihistamines. |
| American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **Disease Management of Atopic Dermatitis: An Updated Practice Parameter[7] (2004)** | General considerations<br>• The management of atopic dermatitis requires multiple therapeutic approaches including antipruritic therapy, skin hydration, topical anti-inflammatory medications, and the identification/elimination of exacerbating factors.<br><br>Skin hydration<br>• Moisturizers followed by the use of occlusive emollients provide symptomatic relief.<br>• Emollients are available as lotions, creams, and ointments, and should be used as first-line therapy.<br><br>Topical corticosteroids<br>• Topical corticosteroids are an effective treatment option for atopic |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | dermatitis.<br>• Low-potency corticosteroids are recommended for maintenance therapy, whereas intermediate-and high-potency corticosteroids should be used for the treatment of exacerbation and applied to affected areas over short periods of time.<br>• Ultrahigh-potency corticosteroids should be used only for very short periods of time (several days) and only in areas that are lichenified.<br><br><u>Topical calcineurin inhibitors</u><br>• Tacrolimus ointment has been shown to be effective for the treatment of mild-to-moderately severe atopic dermatitis.<br>• Tacrolimus ointment applied on up to 100% of the body surface in adults and children has demonstrated sustained efficacy with no significant systemic adverse effects. It can be used safely for facial and eyelid eczema.<br>• Pimecrolimus cream decreases the number of flares of atopic dermatitis, reduces the need for corticosteroids, and controls pruritus.<br><br><u>Tar preparations</u><br>• There are no randomized studies that have demonstrated the efficacy of tar preparations, despite their widespread use for the treatment of atopic dermatitis.<br>• Newer coal tar products have been developed that are more cosmetically acceptable than older products.<br><br><u>Antihistamines</u><br>• Patients may benefit from the use of oral antihistamines for the relief of pruritus associated with atopic dermatitis, especially in those with concomitant urticaria or allergic rhinitis.<br>• Second generation antihistamines may be effective in relieving symptoms of atopic dermatitis.<br>• Pruritus is usually worse at night; therefore, a sedating antihistamine (e.g., hydroxyzine or diphenhydramine) may offer an advantage when used at bedtime.<br>• Treatment of atopic dermatitis with topical antihistamines is generally not recommended because of potential cutaneous sensitization.<br><br><u>Microbes</u><br>• Systemic antibiotics may be considered in patients who are heavily colonized or infected with *staphylococcal aureus*.<br><br><u>Systemic corticosteroids</u><br>• The use of systemic corticosteroids may be required in the treatment of severe, recalcitrant chronic atopic dermatitis.<br><br><u>Systemic immunomodulating agents</u><br>• Immunosuppressive agents such as cyclosporin, interferon gamma, mycophenolate mofetil, and azathioprine have been shown to provide benefit for certain cases of severe refractory atopic dermatitis, but potential benefits should be weighed against their potentially serious adverse effects. |
| American Academy of Ophthalmology (AAO) Preferred Practice Pattern Guidelines: | <u>Seasonal allergic conjunctivitis</u><br>• Mild allergic conjunctivitis can be treated with an over-the-counter antihistamine/vasoconstrictor agent or with the more effective second-generation topical histamine $H_1$- receptor antagonists. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Conjunctivitis[8] (2011)** | • Mast-cell stabilizers can be utilized if the condition is recurrent or persistent.<br>• Combination antihistamine and mast-cell stabilizer medications can be utilized for either acute or chronic disease.<br>• If the symptoms are not adequately controlled, a brief course (one to two weeks) of a low-potency topical corticosteroid can be added to the regimen.<br>• A nonsteroidal anti-inflammatory agent (ketorolac) has been Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis.<br>• Additional measures include the use of artificial tears, cool compresses, oral antihistamines, and allergen avoidance. Frequent clothes washing and bathing/showering before bedtime may also be helpful.<br>• Use of topical mast-cell stabilizers can also be helpful in alleviating symptoms of allergic rhinitis, and intranasal corticosteroids is not effective for the treatment of seasonal allergic conjunctivitis.<br><br>Vernal/atopic conjunctivitis<br>• General treatment measures include minimizing exposure to allergens or irritants, and using cool compresses and ocular lubricants.<br>• Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort.<br>• Topical corticosteroids are usually necessary to control severe signs and symptoms during acute exacerbations.<br>• Topical cyclosporine (2.0%) is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis.<br>• For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, systemic immunosuppression may be warranted rarely.<br>• In patients two years of age and older, eyelids can be treated with pimecrolimus cream (1.0%) or tacrolimus ointment applied to the affected eyelid skin. Both agents are rarely associated with development of skin cancer or lymphoma. |
| American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI):<br>**The Diagnosis and Management of Rhinitis: An Updated Practice Parameter[1] (2008)** | Pharmacologic therapy<br>• The selection of pharmacotherapy depends on multiple factors, including the type of rhinitis present (e.g., allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age.<br><br>Oral antihistamines<br>• First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects.<br>• First-generation antihistamines may produce performance impairment in school and driving that can exist without subjective awareness of sedation. The use of first-generation antihistamines has been associated with increased automobile and occupational accidents.<br>• Due to the prolonged half-life and active metabolites, these adverse effects cannot be eliminated by the administration of first-generation antihistamines only at bedtime.<br>• The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines.<br>• The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | has not been adequately studied.<br>• Before prescribing a first-generation antihistamine, healthcare providers should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects.<br>• Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis because they have a lower tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects.<br>• Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines.<br>• With regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses.<br>• No single second-generation antihistamine has been conclusively shown to have greater efficacy.<br><br><u>Intranasal antihistamines</u><br>• Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis.<br>• Intranasal antihistamines are efficacious and equal to or more effective than oral second-generation antihistamines for treatment of seasonal allergic rhinitis.<br>• Intranasal antihistamines have been associated with sedation and can inhibit skin test reactions due to systemic absorption.<br>• Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion.<br>• Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis.<br><br><u>Oral decongestants</u><br>• Oral decongestants, such as pseudoephedrine and phenylephrine, effectively relieve nasal congestion in patients with allergic and nonallergic rhinitis, but can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations.<br>• The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone.<br>• Pseudoephedrine is a key ingredient used in making methamphetamine and restrictions have been placed on the sale of pseudoephedrine in the United States to reduce illicit production of methamphetamine.<br>• Phenylephrine has been substituted for pseudoephedrine in many over-the-counter products. Phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut. The efficacy of phenylephrine as an oral decongestant has not been well established.<br>• Elevation of blood pressure after taking an oral decongestant is rarely seen in normotensive patients and only occasionally in patients with controlled hypertension.<br>• Concomitant use of caffeine and stimulants may be associated with an increase in adverse events.<br>• Oral decongestants should be used with caution in older adults and young children, and in patients of any age with a history of cardiac |

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| | arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism.<br>• Oral decongestants are usually well tolerated in children over six years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and death. The risks and benefits must be considered before using oral decongestants in children below six years of age.<br><br><u>Topical decongestants</u><br>• Topical decongestants may be considered for the short-term or intermittent/episodic treatment of nasal congestion, but are not recommended for daily use due to the risk of rhinitis medicamentosa.<br><br><u>Intranasal corticosteroids</u><br>• Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis.<br>• Intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene antagonist in the treatment of seasonal allergic rhinitis in most studies.<br>• The clinical response does not appear to vary significantly among the intranasal corticosteroids, despite the differences in topical potency, lipid solubility, and binding affinity.<br>• Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis.<br>• Nasal irritation and bleeding may occur with the use of intranasal corticosteroids. Nasal septal perforation has rarely been reported.<br><br><u>Oral corticosteroids</u><br>• A short course (five to seven days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis.<br>• Single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects.<br><br><u>Intranasal cromolyn</u><br>• Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects.<br>• Intranasal cromolyn is less effective than corticosteroids in most patients and has not been adequately studied in comparison with leukotriene antagonists or antihistamines.<br><br><u>Intranasal anticholinergics</u><br>• Intranasal anticholinergics may effectively reduce rhinorrhea, but have no effect on other nasal symptoms.<br>• Dryness of the nasal membranes may occur with intranasal anticholinergics.<br>• The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased risk of adverse events.<br><br><u>Oral antileukotriene agents</u><br>• Oral antileukotriene agents alone, or in combination with |

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| | antihistamines, have proven to be useful in the treatment of allergic rhinitis.<br><br>Omalizumab<br>• Omalizumab has demonstrated efficacy in allergic rhinitis; however, it only FDA-approved for use in allergic asthma.<br><br>Nasal saline<br>• Topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used alone or as adjunctive therapy.<br><br>Over-the-counter cough and cold medications for young children<br>• The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than six years.<br>• Because of the potential toxicity, the use of these over-the-counter products should be avoided in children below six years of age. |
| Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Respiratory Illness in Children and Adults[9] (2011)** | Allergic rhinitis<br>• Intranasal corticosteroids are the most effective treatment for allergic rhinitis and should be considered first-line therapy in patients with moderate to severe symptoms. Systemic corticosteroid use should be reserved for refractory or severe cases only, and given in short bursts. Injectable corticosteroids are generally not recommended as they are invasive and tend to have a longer duration of action than typical courses of corticosteroids.<br>• Antihistamines are effective at controlling all symptoms associated with allergic rhinitis, with the exception of nasal congestion. They are less effective compared to intranasal corticosteroids, but can be used either on a daily basis or on an as-needed basis.<br>• Second-generation antihistamines are less sedating than first-generation antihistamines, and cause less central nervous system impairment.<br>• Adverse events commonly associated with first-generation antihistamines include somnolence, decreased alertness and anticholinergic effects. These agents may cause central nervous system impairment and impair driving performance.<br>• Oral decongestants reduce nasal congestion and are available in short-acting and sustained-release preparations. Oral decongestants can be a useful addition to antihistamines. Topical decongestants are effective for the short-term relief of nasal congestion, but may induce rebound congestion after three days of use. Topical decongestants are also advantageous for use in very congested noses prior to instilling intranasal corticosteroids.<br>• Cromolyn is less effective compared to intranasal corticosteroids, and is most effective when used regularly prior to the onset of allergic symptoms. Cromolyn is a good alternative for patients who are not candidates for corticosteroids.<br>• Intranasal anticholinergics are effective in relieving anterior rhinorrhea in patients with allergic and non-allergic rhinitis. They have no effect on congestion, sneezing or itching.<br>• Ophthalmic preparations contain antihistamines, decongestants, corticosteroids, combination antihistamines/decongestants, corticosteroids, or mast cell stabilizers. Topical antihistamines can be used as needed for acute symptomatic relief and prophylaxis of allergic rhinitis with minimal systemic side effects. |

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| | Non-allergic rhinitis<br>• Treatment of symptomatic nasal obstruction due to non-allergic rhinitis includes the use of azelastine nasal spray, intranasal corticosteroids, intranasal cromolyn, oral decongestants, nasal strips and topical antihistamines.<br>• Intranasal corticosteroids can be used to treat chronic nasal congestion secondary to non-allergic rhinitis. Intranasal corticosteroids have a relatively long onset of action (up to four weeks) and are therefore better suited to patients with chronic symptoms.<br>• Intranasal cromolyn may improve sneezing and congestion scores, and it can be safely used in children two years of age and older.<br>• Some patients find oral decongestants helpful at relieving symptomatic nasal obstruction secondary to non-allergic rhinitis. Oral decongestants have a relatively rapid onset of action; therefore, are particularly useful for sporadic symptoms. Patients using oral decongestants should be monitored for hypertension.<br>• Nasal strips may be effective for patients with nocturnal symptoms. They are more effective for patients with narrow noses or with anterior septal deviations. Daytime use of nasal strips is not usually practical.<br>• Topical antihistamines have been shown to be effective in controlling rhinorrhea associated with non-allergic rhinitis.<br>• Conservative treatment of symptomatic non-purulent chronic posterior nasal drainage includes increased water intake, decreased caffeine and alcohol intake, nasal saline irrigation, use of petroleum jelly or antibiotic ointment for nasal crusting, and the addition of humidity in bedroom, if significantly less than 50%. In addition, it should be determined if the patient is using any medications that may cause oral or nasal dryness.<br>• Medical treatment of symptomatic non-purulent chronic posterior nasal drainage includes intranasal corticosteroids.<br>• Treatment of symptomatic bilateral chronic anterior rhinorrhea due to non-allergic rhinitis includes avoidance of triggers, intranasal corticosteroids, intranasal ipratropium bromide and nasal saline.<br><br>Bacterial sinusitis<br>• Intranasal corticosteroids may be rational, but is an unproved adjunctive therapy for acute sinusitis. This therapy may be appropriate for selected cases of recurrent sinusitis, especially in the presence of an allergy or inflammation etiology.<br>• Antibiotics should be reserved for those patients who failed decongestant therapy, those we present with symptoms and signs of a more severe illness, and those how have complications of acute sinusitis. |
| Global Allergy and Asthma European Network: **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines: 2010 Revision (2010)**[10] | Pharmacologic treatment of allergic rhinitis<br>• New-generation oral $H_1$-antihistamines that do not cause sedation and do not interact with cytochrome P450 are recommended for allergic rhinitis.<br>• New-generation oral $H_1$-antihistamines are recommended over old-generation oral $H_1$-antihistamines.<br>• In infants with atopic dermatitis and/or family history of allergy or asthma, it is suggested that oral $H_1$-antihistamines not be used to prevent wheezing or asthma.<br>• Intranasal $H_1$-antihistamines are suggested in adults and children with seasonal allergic rhinitis. |

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| | • New-generation oral $H_1$-antihistamines are suggested over intranasal $H_1$-antihistamines in adults with seasonal allergic rhinitis and in adults with persistent allergic rhinitis. The same is suggested for children with intermittent or persistent allergic rhinitis.<br>• Oral leukotriene receptor antagonists are suggested in adults and children with seasonal allergic rhinitis, as well as in preschool children with persistent allergic rhinitis. It is suggested that these agents not be used in adults with persistent allergic rhinitis.<br>• Oral $H_1$-antihistamines are suggested over oral leukotriene receptor antagonists for seasonal allergic rhinitis and in preschool children with persistent allergic rhinitis.<br>• Intranasal glucocorticosteroids are recommended for adults with allergic rhinitis. These agents are suggested in the management of children with allergic rhinitis.<br>• For seasonal and persistent allergic rhinitis, intranasal glucocorticosteroids are suggested over oral $H_1$-antihistamines in adults and children.<br>• Intranasal glucocorticosteroids are recommended over intranasal $H_1$-antihistaimines for allergic rhinitis, and are recommended over oral leukotriene receptor antagonists for seasonal allergic rhinitis.<br>• For treatment refractory allergic rhinitis with moderate to severe nasal and/or ocular symptoms, a short course of oral glucocorticosteroids is suggested.<br>• Intramuscular glucocorticosteroids are not recommended for allergic rhinitis.<br>• Intranasal chromones are suggested for allergic rhinitis, and intranasal $H_1$-antihistamines are suggested over intranasal chromones.<br>• Intranasal ipratropium bromide is suggested for the management of rhinorrhea with persistent allergic rhinitis.<br>• A very short course (no longer than five days and preferably shorter) of intranasal decongestants is suggested for the management of severe nasal obstruction with allergic rhinitis in adults. These agents should be administered with other treatments, and it is suggested that they not be used in preschool children.<br>• It is suggested that regular use of oral decongestants, either alone or in combination with an oral $H_1$-antihistamine, not occur in patients with allergic rhinitis.<br>• Intraocular $H_1$-antihistamines or chromones are suggested for the management of symptoms of conjunctivitis with allergic rhinitis. |
| International Primary Care Respiratory Group (IPCRG) Guidelines: **Management of Allergic Rhinitis[11] (2006)** | <u>Mild intermittent allergic rhinitis</u><br>• Recommended therapy:<br>  ○ Oral $H_1$-blocker.<br>  ○ Intranasal $H_1$-blocker.<br>  ○ Decongestant.<br>  AND/OR<br>  ○ Intranasal saline.<br>• Review patient after two to four weeks. If improved, consider stepping down therapy.<br>• If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe intermittent allergic rhinitis treatment options).<br><br><u>Moderate/severe intermittent allergic rhinitis</u><br>• Recommended therapy: |

| Clinical Guideline | Recommendation(s) |
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| | ○ Oral $H_1$-blocker.<br>○ Intranasal $H_1$-blocker.<br>AND/OR<br>○ Decongestant.<br>○ Intranasal saline.<br>○ Intranasal glucocorticosteroid.<br>○ Mast cell stabilizer.<br>○ Antileukotriene (preferred in patients with coexisting asthma).<br>• Review patient after two to four weeks. If improved, consider stepping down therapy.<br>• If failure, review diagnosis and compliance, query infections and other causes, then consider trial of different treatment option or specialist referral.<br><br><u>Mild persistent allergic rhinitis</u><br>• Recommended therapy:<br>○ Oral $H_1$-blocker.<br>○ Intranasal $H_1$-blocker.<br>AND/OR<br>○ Decongestant.<br>○ Intranasal glucocorticosteroid.<br>○ Intranasal saline.<br>○ Mast cell stabilizer.<br>○ Antileukotriene (preferred in patients with coexisting asthma).<br>• Review patient after two to four weeks. If improved, continue treatment for at least 1 month after symptoms resolve. Consider stepping down dose.<br>• If failure, review diagnosis, review compliance, query infections and other causes, then consider trial of different treatment option or step up therapy (see moderate/severe persistent allergic rhinitis treatment options).<br><br><u>Moderate/severe persistent allergic rhinitis</u><br>• Recommended therapy:<br>○ Intranasal glucocorticosteroid.<br>○ Decongestant.<br>○ Oral $H_1$-blocker.<br>○ Intranasal saline.<br>○ Antileukotriene (preferred in patients with coexisting asthma).<br>• Review patient after two to four weeks. If improved, continue treatment for at least 1 month after symptoms resolve. Consider stepping down dose.<br>• If failure, review diagnosis, review compliance, query infections and other causes, then choose one or more of the following options:<br>○ Increase nasal steroid dose, consider trial of different treatment option, or consider referral to specialist.<br>○ If sneeze/itch: add $H_1$-blocker.<br>○ If rhinorrhea: add ipratropium.<br>○ If blockage: add decongestant or short course of oral steroids.<br><br><u>General treatment considerations</u><br>• First generation $H_1$-antihistamines cause sedation and central nervous system impairment. These side effects may adversely affect cognition, learning and driving. These side effects may be potentiated by alcohol and other sedatives. Adverse events may not always be perceived by patients. |

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| | • Second generation $H_1$-antihistamines are associated with less sedation and impairment than first generation antihistamines.<br>• Intranasal and intraocular $H_1$-antihistamines are as effective as oral antihistamines at the site of their administration.<br>• Intranasal glucocorticosteroids are the most effective class of medications available for the treatment of allergic and nonallergic rhinitis. Oral glucocorticosteroids are rarely needed to control severe symptoms of allergic rhinitis.<br>• Mast cell stabilizers reduce symptoms of allergic rhinitis, but are generally less effective than other treatments and require frequent administration. Ocular mast cell stabilizers are effective and have a role in the treatment of allergic conjunctivitis.<br>• Anticholinergic agents can reduce rhinorrhea, but have little effect on other symptoms of allergic rhinitis.<br>• Antileukotriene agents are effective for the treatment of allergic rhinitis and asthma. They have been shown to be as effective as oral antihistamines, but have a greater effect on nasal obstruction. They may have an additive effect with antihistamines. |
| American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF):<br>**Clinical Practice Guideline: Adult Sinusitis[12] (2007)** | <u>Symptomatic relief of viral rhinosinusitis</u><br>• Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively.<br>• Topical or systemic decongestants may offer additional symptomatic relief.<br>• Antihistamines have been used to treat viral rhinosinusitis due to their drying effect; however, no studies have been published that assess the impact of antihistamines specifically on viral rhinosinusitis outcomes. Adverse effects of antihistamines, especially first-generation $H_1$-antagonists, include drowsiness, behavioral changes, and impaired mucus transport in the nose and sinuses because of drying.<br><br><u>Symptomatic relief of acute bacterial rhinosinusitis</u><br>• Symptomatic treatments for acute bacterial rhinosinusitis include decongestants, corticosteroids, saline irrigation, and mucolytics. None of these products have been approved by the FDA for use in acute rhinosinusitis, and few have data from controlled clinical studies supporting this use.<br>• Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. There are no studies that support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa.<br>• Antihistamines may be considered in patients with acute bacterial rhinosinusitis whose symptoms suggest a significant allergic component.<br><br><u>Watchful waiting for acute bacterial rhinosinusitis</u><br>• Observation without use of antibiotics is an option for selected adults with uncomplicated acute bacterial rhinosinusitis who have mild illness (mild pain and temperature <38.3°C or 101°F).<br><br><u>Choice of antibiotic for acute bacterial rhinosinusitis</u><br>• If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin as first-line therapy for most adults.<br><br><u>Treatment failure for acute bacterial rhinosinusitis</u> |

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| | • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications.<br>• If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy.<br>• If the patient was initially managed with an antibiotic, the clinician should change the antibiotic. |
| American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI):<br>**The Diagnosis and Management of Sinusitis: An Updated Practice Parameter[13] (2005)** | <u>Antibiotics</u><br>• Antibiotics are the primary therapy for bacterial sinusitis.<br>• The most common bacteria observed in acute sinusitis, recurrent acute sinusitis, and acute exacerbations of chronic sinusitis are *S pneumoniae*, *H influenzae*, and *M catarrhalis*.<br>• Amoxicillin often is the drug of choice for children and adults.<br>• Trimethoprim-sulfamethoxazole can be used as an alternative drug in adults.<br>• For patients who do not respond to amoxicillin, high-dose amoxicillin-clavulanate is recommended.<br>• For patients allergic to or intolerant of amoxicillin, alternatives include cephalosporins, macrolides, or quinolones.<br>• The appropriate duration of antibiotic therapy for acute sinusitis is not well defined.<br>• Antibiotic treatment of uncomplicated viral upper respiratory tract infection is inappropriate and discouraged strongly.<br><br><u>Antihistamines</u><br>• There are no data to recommend the use of $H_1$-antihistamines for the treatment of acute bacterial sinusitis.<br>• There may be a role for the use of antihistamines in the treatment of chronic sinusitis if the underlying risk factor is allergic rhinitis.<br><br><u>α-Adrenergic decongestants</u><br>• Topical and oral decongestants are often used to treat acute and chronic sinusitis as they decrease nasal resistance and increase ostial patency; however, additional studies are needed to assess the value of decongestants in the prevention and treatment of sinusitis.<br><br><u>Glucocorticosteroids</u><br>• The addition of intranasal corticosteroids to antibiotic therapy might be modestly beneficial in the treatment of patients with recurrent acute or chronic sinusitis.<br>• The use of systemic corticosteroid therapy for sinus disease has not been well studied.<br><br><u>Adjunctive therapies: saline, mucolytics, and expectorants</u><br>• These agents are commonly used and in some instances might be beneficial in some patients; however, use of all these agents as prophylaxis for exacerbations of chronic sinusitis is empiric and not supported by clinical data.<br>• Saline nasal sprays or lavage might be a useful adjunct by liquefying secretions and decreasing the risk of crusting near the sinus ostia.<br>• There is no conclusive evidence that mucolytics, such as guaifenesin, are useful adjuncts in treating acute sinusitis. |
| British Association of | <u>Antihistamines</u> |

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| Dermatologists (BAD) Therapy Guidelines and Audit Subcommittee: **Guidelines for Evaluation and Management of Urticaria in Adults and Children**[2] **(2007)** | • Antihistamines are effective and safe for the treatment of urticaria; however, not all patients respond and some become worse.<br>• All patients should be offered the choice of at least two nonsedating $H_1$-antihistamines because responses and tolerance vary between individuals.<br>• It has become common practice to increase the dose above the manufacturer's licensed recommendation for patients who do not respond when the potential benefits are considered to outweigh any risks.<br>• The use of sedating antihistamines as monotherapy is now less common because of concerns about reduced concentration and performance, but they can be effective and well tolerated by some individuals.<br>• Doxepin has useful antihistaminic properties, but has sedating and anticholinergic side effects.<br>• Addition of a sedating antihistamine at night (e.g., chlorphenamine, hydroxyzine) to a nonsedating antihistamine by day may help patients sleep better; however, it probably has little additional clinical effect on urticaria if the $H_1$ receptor is already saturated.<br><br><u>Antileukotriene agents</u><br>• Antileukotriene agents may be taken in addition to an $H_1$-antihistamine for poorly controlled urticaria; however, there is little evidence that they are useful as monotherapy.<br>• Antileukotriene agents are more likely to benefit aspirin-sensitive and autologous serum skin test-positive chronic ordinary urticaria than other patterns of urticaria. Montelukast is usually chosen.<br><br><u>Corticosteroids</u><br>• Oral corticosteroids may shorten the duration of acute urticaria.<br>• Parenteral hydrocortisone is often given as an adjunct for severe laryngeal edema and anaphylaxis although its action is delayed. Short courses of oral steroids over three to four weeks may be necessary for urticarial vasculitis and severe delayed pressure urticaria, but long-term oral corticosteroids should not be used in chronic urticaria except in select cases under regular specialist supervision.<br><br><u>Immunomodulating therapies</u><br>• Cyclosporin is the best studied immunosuppressive drug for chronic ordinary urticaria. Optimal patient selection, dose and duration of treatment still need to be defined.<br>• Similar response rates have been seen with tacrolimus and mycophenolate mofetil.<br>• Plasmapheresis and intravenous immunoglobulins may also be effective in severe autoimmune chronic urticaria.<br>• There have been reports of success with methotrexate and cyclophosphamide. |
| American Academy of Allergy, Asthma, and Immunology (AAAAI)/American College of Allergy, Asthma and Immunology (ACAAI)/Joint Council on Allergy, Asthma and Immunology (JCAAI): **Diagnosis and Management of** | <u>Acute urticaria/angioedema</u><br>• Antihistamines are the cornerstone of therapy for acute urticaria and/or angioedema.<br>• Continuous treatment with antihistamines over a period of weeks may suppress the urticarial process until remission occurs.<br>• Second-generation $H_1$-antihistamines may be effective in controlling urticaria with limited adverse effects.<br>• The impact of treatment on mental alertness and quality of life can be |

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| **Urticaria: An Practice Parameter[3] (2000)** | minimized with the use of second-generation $H_1$-antihistamines compared to the use of first-generation $H_1$-antihistamines.<br>• First-generation $H_1$-antihistamines may be added to or given in place of second-generation agents on an as-needed basis to achieve optimal hive and pruritus control.<br>• If optimal doses of $H_1$-antihistamines do not provide adequate hive control, $H_2$-antihistamines (e.g., ranitidine or cimetidine) may be added.<br>• Tricyclic antidepressants (e.g., doxepin), with more potent $H_1$- and $H_2$-antihistamine properties than some first-generation antihistamines, may have a role in therapy, although adverse effects may limit their use.<br>• The routine use of glucocorticosteroids in the treatment of patients with acute urticaria and/or angioedema is rarely necessary. If treatment is required, short courses of oral glucocorticosteroids rather than depot parenteral preparations are preferred.<br><br><u>Chronic angioedema without urticaria</u><br>• Individuals with recurrent angioedema due to anaphylaxis should carry an emergency epinephrine kit.<br>• Treatment of recurrent acute life-threatening attacks of C1esterase inhibitor deficiency is limited and usually supportive in nature.<br>• Some clinicians advocate treatment with plasma infusions or C1esterase inhibitor therapy (not available at the time this guideline was published).<br>• For frequent episodes of angioedema due to C1 esterase deficiency, prophylactic use of anabolic steroids can be considered.<br><br><u>Urticarial vasculitis</u><br>• Antihistamines may be useful in managing the pruritus associated with urticarial vasculitis. Other symptoms of urticarial vasculitis do not generally respond to antihistamines.<br>• Patients with moderate or severe cutaneous disease may require treatment with anti-inflammatory agents (e.g., glucocorticosteroids, indomethacin, colchicine, dapsone, hydroxychloroquine).<br>• Cytotoxic agents (e.g., methotrexate, azathioprine, and cyclophosphamide) may be used to reduce the dose requirements of corticosteroids.<br><br><u>Chronic urticaria with or without angioedema</u><br>• For most patients, symptomatic treatment with $H_1$-antihistamines remains the mainstay of management.<br>• Combinations of antihistamines may be useful in suppressing symptoms. These include (1) first generation $H_1$-antihistamines, (2) combinations of first and second generations using non-sedating agents in the morning and first generation drugs at night, (3) combinations of second generation antihistamines, (4) combination of an agent with both $H_1$ and $H_2$ anti-receptor activity (e.g., doxepin) with a first or second generation antihistamine, and (5) combination of an $H_2$-antihistamine (e.g., cimetidine or ranitidine) with a first or second generation antihistamine.<br>• Sedation from first generation antihistamines may be desirable for reducing the discomfort of pruritus associated with urticaria.<br>• First generation antihistamines may cause adverse effects, including driving impairment, decreased workplace productivity, increased risk |

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| | for occupational accidents, increased risk for falls in nursing home patients, as well as impaired learning and academic performance in children. Patients may not perceive performance impairment and there is no correlation between subjective perception of sedation and objective performance impairment.<br>• Second generation antihistamines (at recommended doses) are associated with minimal risk for the adverse effects associated with first generation antihistamines; however, cetirizine may have mild sedative effects.<br>• Antihistamines may not entirely relieve symptoms of urticaria due to the release of other capillary permeability-inducing mediators. Glucocorticosteroid treatment may be appropriate when antihistamines are not effective.<br>• Alternative treatments may be necessary in refractory chronic urticaria/angioedema. Mast cell degranulation inhibitors (e.g., oral terbutaline, albuterol, ketotifen) may have a role in treatment of refractory conditions. Nifedipine, alone or in combination with antihistamines, may also be effective. Antileukotriene agents may be effective in treating patients with chronic idiopathic urticaria. Oral cyclosporine, colchicine, or dapsone may be helpful in selected cases of severe refractory chronic urticaria/angioedema.<br>• Idiopathic (primary) acquired cold urticaria responds to prophylactic treatment with a variety of first generation antihistamines, second generation antihistamines and tricyclic antidepressants.<br>• Cholinergic urticaria can be treated with various antihistamines.<br>• Delayed pressure urticaria can be treated with first and second generation antihistamines and may require courses of oral glucocorticosteroids or other regimens including dapsone, nonsteroidal anti-inflammatory drugs (NSAIDS), and sulfasalazine.<br>• Exercise-induced urticaria (with or without anaphylaxis) may require prophylactic treatment with first and/or second generation antihistamines to help to reduce the frequency and/or intensity of attacks.<br>• Dermatographism is best managed by patient education and the prophylactic use of antihistamines.<br>• Removal of potential urticarial precipitants such as aspirin, NSAIDS, or alcohol is recommended regardless of the underlying etiology. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the first generation antihistamines are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the First Generation Antihistamines[4]**

| Generic Name(s) | Allergic Reactions to Blood/ Plasma | Allergic Conjunct-ivitis | Allergic Rhinitis | Anaphylactic Reactions[†] | Angio-edema* | Dermato-graphism | Sinusitis | Upper Respiratory Allergies | Upper Respiratory Conditions[‡] | Urticaria* | Vasomotor Rhinitis |
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| **Ethanolamine Derivatives** | | | | | | | | | | | |
| Carbinoxamine | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | | | ✔ | ✔ |
| Clemastine | | | ✔ | | ✔ | | | | | ✔ | |
| Diphenhydramine[§] | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | | | ✔ | ✔ |
| Doxylamine[‖] | | | | | | | | ✔ | | | |
| Phenylephrine and diphenhydramine | | | | | | | | ✔ | ✔ | | |
| **Ethylenediamine Derivatives** | | | | | | | | | | | |
| Phenylephrine and pyrilamine | | | ✔ | | | | | ✔ | ✔ | | |
| **Propylamine Derivatives** | | | | | | | | | | | |
| Brompheniramine | | | ✔ | | | | | ✔ | ✔ | | |
| Chlorpheniramine | | | ✔ | | | | | ✔ | ✔ | | |
| Dexchlorpheniramine | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | | | ✔ | ✔ |
| Phenylephrine and brompheniramine | | | ✔ | | | | | | ✔ | | |
| Phenylephrine and chlorpheniramine | | | ✔ | | | | ✔ | | ✔ | | |
| Phenylephrine, pyrilamine, and chlorpheniramine | | | ✔ | | | | ✔ | | ✔ | | |
| Pseudoephedrine and brompheniramine | | | ✔ | | | | | | ✔ | | |
| Pseudoephedrine and chlorpheniramine | | | ✔ | | | | | | ✔ | | |
| Pseudoephedrine and triprolidine | | | ✔ | | | | | | ✔ | | |

*Mild, uncomplicated allergic skin manifestations.

†Adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.
‡Upper respiratory conditions may include the common cold.
§Diphenhydramine is also approved for Antiparkinsonism and insomnia, and for use as an antitussive.
‖Doxylamine (Unisom®) is also approved for insomnia.

## IV. Pharmacokinetics

The pharmacokinetic parameters of the first generation antihistamines are listed in Table 4. There is insufficient information on the pharmacokinetic properties of the fixed-dose combination products. Therefore, only information on the individual components was included in the table.

**Table 4. Pharmacokinetic Parameters of the First Generation Antihistamines[4,14]**

| Generic Name(s) | Bioavailability (%) | Protein Binding(%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| **Ethanolamine Derivatives** | | | | | |
| Carbinoxamine | Not reported | Not reported | Not reported | Not reported | 10 to 20 |
| Clemastine | 39 | Not reported | Liver | Renal | 21 |
| Diphenhydramine | 65 to 100 | 76 to 85 | Liver (50) | Renal (50 to 65) | 4 to 8 |
| Doxylamine | Good | Not reported | Liver | Not reported | 10 |
| **Ethylenediamine Derivatives** | | | | | |
| Pyrilamine | Not reported | Not reported | Liver | Renal | Not reported |
| **Propylamine Derivatives** | | | | | |
| Brompheniramine | Not reported | Not reported | Liver, extensive | Renal (17) | 12 to 25 |
| Chlorpheniramine | Good | Not reported | Liver, extensive | Renal (50) | 20 |
| Dexchlorpheniramine | Well absorbed | Not reported | Liver, extensive | Renal (50) | 20 |
| Triprolidine | Well absorbed | Not reported | Liver | Renal | 2.1 to 5.0 |
| **Decongestants** | | | | | |
| Phenylephrine | 38 | Not reported | Intestinal wall, extensive; Liver | Renal (80 to 86) | 2 to 3 |
| Pseudoephedrine | Not reported | Not reported | Liver (10 to 30) | Renal (70 to 90) | 9 to 16 |

## V. Drug Interactions

Significant drug interactions with the first generation antihistamines are listed in Table 5. Drug interactions are due to the individual components of the combinations products; therefore, only information on the individual ingredients was included in the table.

**Table 5. Significant Drug Interactions with the First Generation Antihistamines[4]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Clemastine | 1 | Disulfiram | Inhibition of aldehyde dehydrogenase by disulfiram leads to the development of toxic intermediate metabolites. The combination of clemastine and disulfiram may produce acute alcohol intolerance. |
| Dexchlorpheniramine | 1 | Disulfiram | Inhibition of aldehyde dehydrogenase by disulfiram leads to the development of toxic intermediate metabolites. The combination of dexchlorpheniramine and disulfiram may produce acute alcohol intolerance. |
| Sympathomimetics (phenylephrine, pseudoephedrine) | 1 | Linezolid | Pharmacologic effects of sympathomimetics may be increased by linezolid. Headache, hyperpyrexia, and hypertension may occur. |
| Clemastine | 2 | Metronidazole | Metronidazole may inhibit aldehyde dehydrogenase-medicated metabolism of ethanol and cause a toxic accumulation of |

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| | | | acetaldehyde. The combination of metronidazole and clemastine may produce alcohol intolerance reactions. |
| Dexchlorpheniramine | 2 | Metronidazole | Metronidazole may inhibit aldehyde dehydrogenase-medicated metabolism of ethanol and cause a toxic accumulation of acetaldehyde. The combination of metronidazole and dexchlorpheniramine may produce alcohol intolerance reactions. |
| Diphenhydramine | 2 | Beta-adrenergic blockers | Inhibition of cytochrome P450 2D6 isoenzyme-mediated metabolism by diphenhydramine may decrease the elimination of beta-adrenergic blockers. Plasma concentrations and cardiovascular effects of beta-adrenergic blockers may be increased when co-administered with diphenhydramine. |
| First generation antihistamines | 2 | Sodium oxybate | The pharmacologic effects of sodium oxybate and first generation antihistamines may be additive. Concurrent use of sodium oxybate and first generation antihistamines may result in an increase in sleep duration and central nervous system depression. |
| Phenylephrine | 2 | Catechol-O-methyl transferase (COMT) inhibitors | The use of sympathomimetics in combination with COMT inhibitors may result in inhibition of the major pathway responsible for normal catecholamine metabolism. Excessive sympathetic stimulation may result. |
| Phenylephrine | 2 | Tricyclic antidepressants | Tricyclic antidepressants interfere with the neuronal uptake of sympathomimetic amines. Alpha-adrenergic (vascular) effects of direct-acting sympathomimetics may be increased; effects of indirect-acting sympathomimetics may be decreased. |

Significance Level 1 = major severity.
Significance Level 2 = moderate severity.

## VI. Adverse Drug Events

The most common adverse drug events reported with the first generation antihistamines are listed in Table 6. These agents have the potential to cause sedation, performance impairment and anticholinergic adverse effects.[14]

**Table 6. Adverse Drug Events (%) Reported with the First Generation Antihistamines[14]**

| Adverse Events | Ethanolamine Derivatives | | | | Ethyl-enediamine Derivatives | Propylamine Derivatives | | | | Decongestants | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carbinox-amine | Clem-astine | Diphen-hydramine | Doxy-lamine | Pyrilamine | Brom-phen-iramine | Chlor-phen-iramine | Dexchlor-phen-iramine | Triprol-idine | Phenyl-ephrine | Pseudo-ephedrine |
| **Cardiovascular** | | | | | | | | | | | |
| Arrhythmias | - | - | - | - | - | - | - | - | - | ✔ | - |
| Atrial fibrillation | - | - | - | - | - | - | - | - | - | - | ✔ |
| Bradyarrhythmia | - | ✔ | - | - | - | - | - | - | - | - | - |
| Cardiac dysrhythmia | - | - | - | - | - | - | ✔ | ✔ | - | - | - |
| Cardiovascular finding | - | - | ✔ | - | - | - | - | - | - | - | ✔ |
| Extrasystoles | - | - | - | - | - | - | - | - | ✔ | - | - |
| Hypertension | - | - | - | - | - | - | - | - | ✔ | ✔ | ✔ |
| Hypotension | - | - | - | - | - | - | ✔ | - | ✔ | - | ✔ |
| Myocardial infarction | - | - | - | - | - | - | - | - | - | ✔ | ✔ |
| Myocardial perfusion | - | - | - | - | - | - | - | - | - | ✔ | - |
| Palpitations | - | - | - | - | ✔ | - | - | - | ✔ | - | - |
| Pulmonary edema | - | - | - | - | - | - | - | - | - | ✔ | - |
| Raynaud's phenomenon | - | - | ✔ | - | - | - | - | - | - | - | - |
| Tachycardia | - | - | - | - | - | - | - | - | ✔ | ✔ | - |
| Ventricular premature beats | - | - | - | - | - | - | - | - | - | - | ✔ |
| **Central Nervous System** | | | | | | | | | | | |
| Anxiety | - | - | - | - | - | - | - | - | - | ✔ | ✔ |
| Aseptic meningitis | - | - | - | - | - | - | - | ✔ | - | - | - |
| Ataxia | - | ✔ | - | - | - | - | - | - | - | - | - |
| Auditory attention | - | - | - | - | - | - | - | ✔ | - | - | - |

| Adverse Events | Ethanolamine Derivatives | | | | Ethyl-enediamine Derivatives | Propylamine Derivatives | | | | Decongestants | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carbinox-amine | Clem-astine | Diphen-hydramine | Doxy-lamine | Pyrilamine | Brom-phen-iramine | Chlor-phen-iramine | Dexchlor-phen-iramine | Triprol-idine | Phenyl-ephrine | Pseudo-ephedrine |
| Central nervous system stimulation | - | ✔ | - | - | ✔ | - | - | - | - | - | - |
| Dizziness | ✔ | ✔ | - | - | - | - | - | - | ✔ | - | - |
| Drowsiness | - | ✔ | - | - | ✔ | ✔ | - | - | - | - | - |
| Dyskinesia | - | - | ✔ | - | - | ✔ | ✔ | ✔ | - | - | - |
| Dystonia | - | - | ✔ | - | - | - | - | - | - | - | - |
| Electro-encephalograph finding | - | - | - | - | - | - | ✔ | ✔ | - | - | - |
| Encephalopathy | - | - | ✔ | - | ✔ | - | - | - | - | - | - |
| Fatigue | ✔ | ✔ | - | - | - | - | - | - | ✔ | - | - |
| Headache | ✔ | ✔ | - | - | - | - | - | ✔ | - | - | - |
| Hypesthesia | - | - | - | - | - | - | - | - | - | ✔ | - |
| Incoordination | - | - | - | - | - | - | - | - | ✔ | - | - |
| Insomnia | - | - | - | - | ✔ | ✔ | - | - | ✔ | ✔ | ✔ |
| Irritability | - | - | - | - | - | ✔ | - | - | ✔ | - | ✔ |
| Lassitude | - | - | - | - | - | - | - | - | ✔ | - | - |
| Nervousness | ✔ | - | - | - | ✔ | ✔ | - | - | ✔ | ✔ | ✔ |
| Neurological finding | - | - | ✔ | ✔ | - | - | - | - | - | - | - |
| Nightmares | - | - | - | - | - | - | - | - | ✔ | - | - |
| Myofascial pain | - | - | - | - | - | - | - | - | - | ✔ | - |
| Restlessness | - | - | - | - | - | - | - | - | ✔ | - | ✔ |
| Sedation | ✔ | - | - | - | ✔ | - | ✔ | - | ✔ | - | - |
| Seizures | - | - | - | - | - | - | - | - | ✔ | - | ✔ |
| Somnolence | - | ✔ | ✔ | - | - | - | ✔ | ✔ | ✔ | - | - |
| Tremors | - | - | - | - | ✔ | - | - | - | - | - | - |
| Vertigo | - | ✔ | - | - | - | - | - | - | - | - | - |
| **Dermatologic** | | | | | | | | | | | |
| Bullae | - | - | - | - | - | - | - | - | - | - | - |
| Contact dermatitis | ✔ | - | - | - | - | - | ✔ | ✔ | - | ✔ | ✔ |
| Dermatitis | - | - | ✔ | - | - | - | - | - | - | - | - |
| Dermatologic | - | - | ✔ | - | - | - | - | - | - | - | ✔ |

| Adverse Events | Ethanolamine Derivatives | | | | Ethyl-enediamine Derivatives | Propylamine Derivatives | | | | Decongestants | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carbinox-amine | Clem-astine | Diphen-hydramine | Doxy-lamine | Pyrilamine | Brom-phen-iramine | Chlor-phen-iramine | Dexchlor-phen-iramine | Triprol-idine | Phenyl-ephrine | Pseudo-ephedrine |
| finding | | | | | | | | | | | |
| Fixed drug eruption | - | - | - | - | - | - | - | - | - | - | ✔ |
| Pseudoscarlatina | - | - | - | - | - | - | - | - | - | - | ✔ |
| Phototoxicity | - | - | ✔ | - | - | - | - | - | - | - | - |
| Pruritus | - | ✔ | - | - | - | - | - | - | - | - | - |
| Rash | - | ✔ | - | - | - | - | - | - | - | - | - |
| Sensitization | - | - | - | - | ✔ | - | - | - | - | - | - |
| **Endocrine/Metabolic Effects** | | | | | | | | | | | |
| Acute intermittent porphyria | - | ✔ | ✔ | - | - | - | - | - | - | - | - |
| Hyperthermia | - | - | - | - | - | - | - | - | - | - | ✔ |
| **Gastrointestinal** | | | | | | | | | | | |
| Abdominal discomfort | - | - | - | - | ✔ | - | - | - | ✔ | - | - |
| Anorexia | ✔ | - | - | - | ✔ | - | ✔ | ✔ | ✔ | - | - |
| Constipation | - | - | - | - | ✔ | - | ✔ | ✔ | - | - | - |
| Diarrhea | ✔ | - | - | - | ✔ | - | ✔ | ✔ | - | - | - |
| Disorder of taste | - | - | - | - | - | - | - | - | - | - | ✔ |
| Dry mouth | ✔ | ✔ | - | - | ✔ | - | - | ✔ | ✔ | - | - |
| Epigastric distress | - | - | - | - | - | - | ✔ | ✔ | - | - | - |
| Gastric pain | - | ✔ | - | - | - | - | - | - | - | - | - |
| Gastrointestinal tract finding | - | - | - | - | - | - | - | - | - | - | ✔ |
| Heartburn | ✔ | - | - | - | - | - | - | - | - | - | - |
| Ischemic colitis | - | - | - | - | - | - | - | - | - | - | ✔ |
| Nausea | ✔ | ✔ | - | - | ✔ | - | ✔ | ✔ | ✔ | - | - |
| Vomiting | ✔ | ✔ | - | - | ✔ | - | ✔ | ✔ | ✔ | - | - |
| Xerostomia | - | - | - | - | - | ✔ | - | - | - | - | - |
| **Hematologic** | | | | | | | | | | | |
| Agranulocytosis | - | - | - | - | - | ✔ | ✔ | ✔ | - | - | - |
| Aplastic anemia | - | - | - | - | - | - | ✔ | ✔ | - | - | - |
| Leukocytosis | - | - | - | - | - | - | - | - | - | ✔ | - |
| Thrombocytopenia | - | - | - | - | - | - | ✔ | ✔ | - | - | - |

| Adverse Events | Ethanolamine Derivatives | | | | Ethyl-enediamine Derivatives | Propylamine Derivatives | | | | Decongestants | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carbinox-amine | Clem-astine | Diphen-hydramine | Doxy-lamine | Pyrilamine | Brom-phen-iramine | Chlor-phen-iramine | Dexchlor-phen-iramine | Triprol-idine | Phenyl-ephrine | Pseudo-ephedrine |
| **Immunologic** | | | | | | | | | | | |
| Anaphylaxis | - | - | ✔ | - | - | - | - | - | - | - | - |
| Cell-mediated immune reaction | - | - | - | - | - | - | - | - | - | ✔ | - |
| Immune hypersensitivity reaction | - | - | ✔ | - | - | - | - | - | - | - | - |
| Immune system finding | - | - | ✔ | - | - | - | - | - | - | - | - |
| **Musculoskeletal** | | | | | | | | | | | |
| Fracture of bone | - | - | ✔ | - | - | - | - | - | - | - | - |
| Musculoskeletal finding | - | - | ✔ | - | - | - | - | - | - | - | - |
| Myasthenia gravis | - | - | ✔ | - | - | - | - | - | - | - | - |
| **Ophthalmic** | | | | | | | | | | | |
| Aqueous pigment floater | - | - | - | - | - | - | - | - | - | ✔ | - |
| Blurred vision | - | - | - | - | ✔ | ✔ | - | - | ✔ | - | - |
| Conjunctivitis | - | - | - | - | - | - | - | - | - | ✔ | - |
| Diplopia | ✔ | - | - | - | - | - | - | - | ✔ | - | - |
| Miosis | - | - | - | - | - | - | - | - | - | ✔ | - |
| Mydriasis | - | - | - | - | - | - | - | - | - | ✔ | - |
| Visual disturbances | - | - | - | - | ✔ | - | - | - | ✔ | - | - |
| **Psychiatric** | | | | | | | | | | | |
| Agitation | ✔ | - | - | - | - | - | - | - | - | - | ✔ |
| Confusion | - | - | - | - | - | - | - | - | - | - | ✔ |
| Delirium | - | - | - | - | - | - | - | - | ✔ | - | - |
| Euphoria | - | - | - | - | ✔ | - | - | - | ✔ | - | - |
| Excitability | ✔ | - | ✔ | - | ✔ | - | - | - | ✔ | - | - |
| Hallucinations | ✔ | - | - | - | - | - | ✔ | ✔ | ✔ | ✔ | ✔ |
| Hyperactive behavior | - | - | - | - | - | - | - | - | - | - | ✔ |
| Motor nervous | - | - | ✔ | - | - | - | - | - | - | - | - |

| Adverse Events | Ethanolamine Derivatives | | | | Ethyl-enediamine Derivatives | Propylamine Derivatives | | | | Decongestants | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carbinox-amine | Clem-astine | Diphen-hydramine | Doxy-lamine | Pyrilamine | Brom-phen-iramine | Chlor-phen-iramine | Dexchlor-phen-iramine | Triprol-idine | Phenyl-ephrine | Pseudo-ephedrine |
| system finding | | | | | | | | | | | |
| Panic | - | - | - | - | - | - | - | - | - | ✔ | - |
| Paranoid delusions | - | - | - | - | - | - | - | - | - | ✔ | - |
| Psychiatric sign or symptom | - | - | ✔ | - | - | - | - | - | - | - | - |
| Psychosis | - | - | - | - | - | - | - | - | - | ✔ | - |
| Psychotic disorder | - | - | ✔ | - | - | - | - | - | ✔ | - | ✔ |
| Screaming | - | - | - | - | - | - | - | - | - | - | ✔ |
| Toxic psychosis | - | - | - | - | - | - | - | - | - | ✔ | - |
| **Renal** | | | | | | | | | | | |
| Dysuria | ✔ | - | - | - | - | - | - | - | ✔ | - | - |
| Polyuria | ✔ | - | - | - | - | - | - | - | - | - | - |
| Urinary retention | - | - | - | - | - | - | - | - | ✔ | - | - |
| Urogenital finding | ✔ | - | - | - | - | - | - | - | - | - | - |
| **Reproductive** | | | | | | | | | | | |
| Impotence | - | - | - | - | - | - | - | - | ✔ | - | - |
| **Respiratory** | | | | | | | | | | | |
| Hemorrhagic nasal secretions | - | - | - | - | - | - | - | ✔ | - | - | - |
| Nasal dryness | ✔ | - | - | - | - | - | - | ✔ | - | - | - |
| Nasal stiffness | - | - | - | - | - | ✔ | - | - | - | - | - |
| Pulmonary edema | - | - | - | - | - | - | - | - | - | ✔ | - |
| Pulmonary embolism | - | - | - | - | - | - | - | - | - | ✔ | - |
| Respiratory finding | - | - | ✔ | - | - | - | - | - | - | - | - |
| Shortness of breath | - | ✔ | - | - | - | - | - | - | - | - | - |
| Tightness of the chest | - | - | - | - | - | ✔ | - | - | ✔ | - | - |
| Wheezing | - | - | - | - | - | ✔ | - | - | ✔ | - | - |
| **Other** | | | | | | | | | | | |
| Anticholinergic effects | - | - | ✔ | - | - | - | - | - | - | - | - |
| Carcinogen effect | - | - | - | ✔ | - | - | - | - | - | - | - |

| Adverse Events | Ethanolamine Derivatives | | | | Ethyl-enediamine Derivatives | Propylamine Derivatives | | | | Decongestants | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carbinox-amine | Clem-astine | Diphen-hydramine | Doxy-lamine | Pyrilamine | Brom-phen-iramine | Chlor-phen-iramine | Dexchlor-phen-iramine | Triprol-idine | Phenyl-ephrine | Pseudo-ephedrine |
| Death | - | - | ✔ | - | - | - | - | - | - | - | - |
| Drug abuse | - | - | ✔ | - | - | - | - | - | - | - | - |
| Drug dependence | - | - | ✔ | - | - | - | - | - | - | - | - |
| Sense of smell altered | - | - | - | - | - | - | - | - | - | ✔ | - |
| Withdrawal sign or symptom | - | - | ✔ | - | - | - | - | - | - | - | - |

✔ Percent not specified.
- Event not reported.

## VII. Dosing and Administration

The usual dosing regimens for the first generation antihistamines are listed in Table 7. Due to the differences in dosing with the various salt formulations, the products have been further classified by salt formulation in this table when necessary.

**Table 7. Usual Dosing Regimens for the First Generation Antihistamines[15-32]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Ethanolamine Derivatives** | | | |
| Carbinoxamine | Allergic rhinitis and other allergic conditions:<br>Liquid, tablet: 4 to 8 mg three to four times daily | Allergic rhinitis and other allergic conditions:<br>Liquid, tablet: ≥6 years of age: 4 to 6 mg three to four times daily<br><br>Liquid: 3 to 6 years of age: 2 to 4 mg three to four times daily; 2 to 3 years of age: 2 mg three to four 4 times daily | Liquid:<br>4 mg/5 mL<br><br>Tablet:<br>4 mg |
| Clemastine | Allergic rhinitis:<br>Syrup, tablet: initial, 1.34 mg two times daily; maximum, 8.04 mg/day<br><br>Allergic urticaria and angioedema:<br>Syrup, tablet: initial, 2.68 mg one to three times daily; maximum, 8.04 mg/day<br><br>Upper respiratory conditions:<br>Syrup, tablet: 1.34 mg two times daily; maximum, 2.68 mg/day | Allergic rhinitis:<br>Syrup, tablet: ≥12 years of age: initial, 1.34 mg two times daily; maximum, 8.04 mg/day; 6 to <12 years of age: initial, 0.67 mg two times daily; maximum, 4.02 mg/day<br><br>Allergic urticaria and angioedema:<br>Syrup, tablet: ≥12 years of age: initial, 2.68 mg one to three times daily; maximum, 8.04 mg/day; 6 to <12 years of age: initial, 1.34 mg two times daily; maximum, 4.02 mg/day<br><br>Upper respiratory conditions:<br>Syrup, tablet: ≥12 years of age: 1.34 mg two times daily; maximum, 2.68 mg/day | Syrup:<br>0.67 mg/5 mL<br><br>Tablet:<br>1.34 mg |
| Diphenhydramine | Allergic rhinitis and upper respiratory conditions:<br>Oral: 25 to 50 mg four to six times daily; maximum, 300 mg/day<br><br>Antitussive:<br>Oral: 25 mg six times daily; maximum, 150 mg/day<br><br>Insomnia:<br>Oral: 50 mg at bedtime<br><br>Motion sickness:<br>Oral: 25 to 50 mg four to six times daily; maximum, 300 mg/day | Allergic rhinitis and upper respiratory conditions:<br>Oral: ≥12 years of age: 25 to 50 mg four to six times daily; maximum, 300 mg/day; 6 to <12 years of age: 12.5 to 25 mg four to six times daily; maximum, 150 mg/day; 2 to <6 years of age: 6.25 mg four to six times daily; maximum, 37.5 mg/day<br><br>Antitussive:<br>Oral: ≥12 years of age: 25 to 50 mg four to six times daily; maximum, 300 mg/day; 6 to <12 years of age: 12.5 mg six times daily; maximum, 75 mg/day; 2 to <6 years of age: 6.25 mg six | Capsule:<br>25 mg<br>50 mg<br><br>Elixir:<br>12.5 mg/5 mL<br><br>Injection:<br>50 mg/mL<br><br>Liquid:<br>12.5 mg/5 mL<br><br>Syrup:<br>12.5 mg/5 mL<br><br>Tablet:<br>25 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | Parkinsonian syndrome:<br>Oral: initial, 25 mg three times daily; maintenance, 50 mg four times daily<br><br>Other:<br>Injection: 10 to 15 mg IM or IV; maximum, 400 mg/day | times daily; maximum, 37.5 mg/day<br><br>Motion sickness:<br>Oral: ≥12 years of age: 25 to 50 mg four to six times daily; maximum, 300 mg/day; 6 to <12 years of age: 12.5 to 25 mg 30 to 60 minutes prior to travel and four to six times daily; maximum, 150 mg/day; 2 to <6 years of age: 6.25 mg 30 to 60 minutes prior to travel and four to six times daily; maximum, 37.5 mg/day<br><br>Insomnia:<br>Oral: 2 to 12 years of age: 1 mg/kg 30 minutes prior to bedtime; maximum, 50 mg/day<br><br>Other:<br>Injection: 5 mg/kg/day or 150 mg/m$^2$ IM or IV; maximum, 300 mg/day | Tablet (chewable): 12.5 mg |
| Doxylamine | Antihistamine:<br>Tablet (chewable): 7.5 to 12.5 mg four to six times daily; maximum, 75 mg/day<br><br>Insomnia:<br>Tablet (chewable): 25 mg 30 minutes prior to bedtime | Antihistamine:<br>Tablet (chewable): ≥12 years of age: 7.5 to 12.5 mg four to six times daily; maximum, 75 mg/day; 6 to <12 years of age: 3.75 to 6.25 mg four to six times daily; maximum, 37.5 mg/day; 2 to <6 years of age: 1.9 to 3.125 mg four to six times daily; maximum, 18.75 mg/day<br><br>Insomnia:<br>Tablet (chewable): >12 years of age: 25 mg 30 minutes prior to bedtime | Tablet (chewable): 5 mg |
| Phenylephrine tannate and diphenhydramine tannate | Upper respiratory allergies and upper respiratory conditions:<br>Tablet (chewable): 5-12.5 to 10-25 mg four times daily | Upper respiratory allergies and upper respiratory conditions:<br>Tablet (chewable): ≥12 years of age: 5-12.5 to 10-25 mg four times daily; 6 to <12 years of age: 2.5-6.25 to 5-12.5 mg four times daily | Tablet (chewable): 5-12.5 mg |
| **Ethylenediamine Derivatives** | | | |
| Phenylephrine HCl and pyrilamine maleate | Antihistamine/Decongestant:<br>Suspension: 5-16 to 10-32 mg four times daily; maximum, four teaspoons per day<br><br>Tablet: 10-25 mg four to six times daily; maximum, six tablets per day | Antihistamine/Decongestant:<br>Suspension: ≥12 years of age: 5-16 to 10-32 mg four times daily; maximum, four teaspoons per day; 6 to <12 years of age: 5-16 mg four times daily; maximum, four teaspoons per day<br><br>Tablet: ≥12 years of age: 10-25 | Suspension: 5-16 mg/5 mL<br><br>Tablet: 10-25 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | | mg four to six times daily; maximum, six tablets per day; 6 to <12 years of age: 5-12.5 mg four to six times daily; maximum, three tablets per day | |
| Phenylephrine tannate and pyrilamine tannate | Antihistamine/Decongestant: Suspension: 5-16 to 10-32 mg four times daily; maximum, four teaspoons per day | Antihistamine/Decongestant: Suspension: ≥12 years of age: 5-16 to 10-32 mg four times daily; maximum, four teaspoons per day; 6 to <12 years of age: 5-16 mg four times daily; maximum, four teaspoons per day | Suspension: 5-16 mg/5 mL |
| **Propylamine Derivatives** | | | |
| Brompheniramine maleate | Antihistamine: Drops: 4 mg six times daily; maximum, 12 mg/day | Antihistamine: Drops: ≥12 years of age: 4 mg six times daily; maximum, 12 mg/day; 6 to <12 years of age: 2 mg six times daily; maximum, 12 mg/day; 2 to <6 years of age: 1 mg six times daily; maximum, 6 mg/day | Drops: 1 mg/mL |
| Chlorpheniramine maleate | Allergic rhinitis: Syrup, tablet: 4 mg four to six times daily; maximum, 24 mg/day<br><br>Extended release tablet: 12 mg two times daily | Allergic rhinitis: Syrup, tablet: ≥12 years of age: 4 mg four to six times daily; maximum, 24 mg/day; 6 to <12 years of age: 2 mg four to six times daily; maximum, 12 mg/day; 2 to <6 years of age: 1 mg four to six times daily; maximum, 6 mg/day<br><br>Extended release tablet: >12 years of age: 12 mg two times daily | Extended release tablet: 12 mg<br><br>Syrup: 2 mg/5 mL<br><br>Tablet: 4 mg |
| Dexchlorphenira mine maleate | Antihistamine: Syrup: 2 mg four to six times daily | Antihistamine: Syrup: ≥12 years of age: 2 mg four to six times daily; 6 to <12 years of age: 1 mg four to six times daily; 2 to <6 years of age: 0.5 mg four to six times daily | Syrup: 2 mg/5 mL |
| Phenylephrine HCl and brompheniramine maleate | Antihistamine/Decongestant: Suspension: 6-3.6 mg four to six times daily | Antihistamine/Decongestant: Suspension: ≥12 years of age: 6-3.6 mg four to six times daily; 6 to <12 years of age: 3-1.8 mg four to six times daily | Suspension: 10-6 mg/5 mL |
| Phenylephrine HCl and chlorpheniramine maleate | Antihistamine/Decongestant: Drops (2-1 mg/mL): four drops four to six times daily; maximum, six drops per day<br><br>Liquid: 10-4 mg six times daily; maximum, six teaspoons per day | Antihistamine/Decongestant: Drops (2-1 mg/mL): ≥12 years of age: four drops four to six times daily; maximum, six drops per day; 6 to <12 years of age: two drops four to six times daily; maximum, six drops per day<br><br>Drops (2.5-1 mg/mL): 6 to 12 years of age: two drops four to six times daily; 2 to 6 years of age: one drop four to six times daily | Drops: 2-1 mg/mL 2.5-1 mg/mL 3.5-1 mg/mL 5-2 mg/mL*<br><br>Liquid: 10-4 mg/5 mL<br><br>Tablet: 10-4 mg* |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | | Drops (3.5-1 mg/mL): 6 to <12 years of age: one drop four to six times daily; maximum, six drops per day<br><br>Liquid: ≥12 years of age: 10-4 mg six times daily; maximum, six teaspoons per day; 6 to <12 years of age: 5-2 mg six times daily; maximum six teaspoons per day | |
| Phenylephrine HCl, pyrilamine tannate, and chlorpheniramine maleate | Antihistamine/Decongestant: No dosing information is available in the various drug databases. | Antihistamine/Decongestant: No dosing information is available in the various drug databases. | Suspension: 2.5-7.5-10 mg/5 mL |
| Pseudoephedrine HCl and brompheniramine maleate | Antihistamine/Decongestant: No dosing information is available in the various drug databases. | Antihistamine/Decongestant: Drops: 6 to 12 years of age: two drops four to six times daily; maximum, 12 drops per day; 2 to 6 years of age: one drop four to six times daily; maximum, six drops per day | Drops: 7.5-1 mg/mL<br><br>Liquid: 15-1 mg/5 mL* |
| Pseudoephedrine HCl and chlorpheniramine maleate | Antihistamine/Decongestant: Liquid: 60-4 mg four to six times daily<br><br>Tablet: 60-4 mg four to six times daily; maximum, four tablets per day | Antihistamine/Decongestant: Drops: 6 to <12 years of age: two drops four to six times daily; maximum, eight drops per day<br><br>Liquid: ≥12 years of age: 60-4 mg four to six times daily; 6 to <12 years of age 30-2 mg four to six times daily<br><br>Tablet: ≥12 years of age: 60-4 mg four to six times daily; maximum, four tablets per day | Drops: 9-0.8 mg/mL<br><br>Liquid: 30-2 mg/5 mL<br><br>Tablet: 60-4 mg |
| Pseudoephedrine HCl and triprolidine HCl | Antihistamine/Decongestant: Liquid: 26.7-2.5 mg four to six times daily<br><br>Syrup, tablet: 60-2.5 mg four times daily | Antihistamine/Decongestant: Liquid: ≥12 years of age: 26.7-2.5 mg four to six times daily; 6 to <12 years of age: 13.3-1.25 mg four to six times daily<br><br>Syrup, tablet: ≥12 years of age: 60-2.5 mg four times daily | Liquid: 10-0.938 mg/mL<br><br>Syrup: 30-1.25 mg/5 mL<br><br>Tablet: 60-2.5 mg |

HCl=hydrochloride
IM=intramuscular
IV=intravenous
*No dosing information is available in the various drug databases.

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the first generation antihistamines are summarized in Table 8.

**Table 8. Comparative Clinical Trials with the First Generation Antihistamines**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Allergic Rhinitis** | | | | |
| Druce et al.[33] (1998)<br><br>Brompheniramine ER 12 mg BID<br><br>vs<br><br>loratadine10 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients >12 years of age with allergic rhinitis | N=338<br><br>7 days | Primary:<br>Global evaluation scores, evaluation of symptom relief, total symptom severity scores, nasal symptom scores, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>At day three and day seven, physician and subject global evaluation scores for brompheniramine were significantly better than those for loratadine (P<0.001) and placebo (P<0.001). Loratadine was more effective than placebo; however, this was not statistically significant.<br><br>On the subjects' daily overall evaluations of symptom relief, brompheniramine was significantly better than loratadine and placebo on all seven days (P value not reported). Loratadine was significantly better than placebo on day four.<br><br>The total symptom severity scores improved to a greater degree with brompheniramine compared to loratadine or placebo at day three, day seven, and the average over the two visits (P<0.05). Treatment with loratadine improved symptoms to a greater degree than placebo (P<0.05 only when symptoms were averaged over day three and day seven). The mean individual symptom severity scores paralleled the pattern seen for the summed symptom severity scores in the three groups.<br><br>Improvement in nasal symptoms was significantly greater in the patients taking brompheniramine than in those taking loratadine (P<0.01) or placebo (P<0.001) at day three, day seven, and when averaged over the two visits. Improvement in nasal symptoms in the loratadine treatment group was greater than that in the placebo treatment group at day three (P<0.05).<br><br>At visit two, adverse events were reported by 53% of the patients taking brompheniramine, 33% of those taking loratadine, and 36% of those taking placebo (P=0.006). At visit three, adverse events were reported by 34% of the patients taking brompheniramine, 20% of those taking loratadine, and 29% of those taking placebo (P=0.05). At visit two, the |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | frequency of somnolence was 28, 9, and 6% in the brompheniramine, loratadine, and placebo groups, respectively (P<0.001). At visit three, the frequency of somnolence was reduced to 10, 2, and 3% for the brompheniramine, loratadine, and placebo groups, respectively (P=0.011).<br><br>Secondary:<br>Not reported |
| Crawford et al.[34] (1998)<br><br>Chlorpheniramine 8 mg BID for 2 weeks<br><br>vs<br><br>astemizole 10 mg QD for 2 weeks<br><br>vs<br><br>loratadine 10 mg QD for 2 weeks<br><br>vs<br><br>terfenadine† 60 mg BID for 2 weeks<br><br>Pseudoephedrine 60 mg every 8 hours as needed was permitted throughout the study. | OL, XO<br><br>Patients with perennial allergic rhinitis | N=14<br><br>8 weeks | Primary:<br>Nasal-examination score, rhinitis symptom score, overall efficacy score, pseudoephedrine use, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>The physician assessed nasal-examination score for each of the four antihistamines was significantly better than the baseline nasal-examination score (P<0.05).<br><br>The nasal-examination score for astemizole was significantly better than loratadine (P<0.05). No other significant differences in nasal-examination score were noted among the treatment groups.<br><br>There were no significant differences among antihistamines when comparing patient-reported rhinitis symptom scores, overall efficacy scores, or pseudoephedrine use.<br><br>Sedation was noted most frequently by patients taking chlorpheniramine. Headache was the most frequent adverse event with terfenadine.<br><br>Secondary:<br>Not reported |
| von Maur et al.[35] (1985) | OL | N=782 | Primary:<br>Patient preference | Primary:<br>The order of antihistamine preference was chlorpheniramine, |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Chlorpheniramine 2 to 4 mg QID for 2 weeks<br><br>vs<br><br>diphenhydramine 12.5 to 25 mg QID for 2 weeks<br><br>vs<br><br>hydroxyzine 10 to 25 mg QID for 2 weeks<br><br>vs<br><br>tripelennamine† 37.5 to 50 mg TID for 2 weeks<br><br>vs<br><br>trimeprazine† 2.5 mg TID for 2 weeks | Adults and children with seasonal or perennial allergic rhinitis | 5 years | and long-term choice of antihistamine<br><br>Secondary:<br>Not reported | diphenhydramine, tripelennamine, hydroxyzine, and trimeprazine (P<0.001).<br><br>At the end of one year, 78% of patients remained on their preferred antihistamine. By three years, 71% of patients were still on the antihistamine of first choice. By five years, 57% of patients were still on the antihistamine class that had been selected five years before.<br><br>Secondary:<br>Not reported |
| Prevost et al.[36] (1994)<br><br>Chlorpheniramine 12 mg and pseudoephedrine 120 mg BID<br><br>vs | DB, MC, PG, RCT<br><br>Patients 18 to 65 years of age with seasonal allergic rhinitis | N=134<br><br>14 days | Primary:<br>Nasal and non-nasal symptoms<br><br>Secondary:<br>Not reported | Primary:<br>There was a significant decrease from baseline in mean TTSs in both treatment groups (P<0.01).<br><br>On day three, improvement in mean TSS was 54% in the loratadine/pseudoephedrine group and 57% in the chlorpheniramine /pseudoephedrine group. On day 14, there was a 65% improvement in the patients treated with loratadine/pseudoephedrine and 64% improvement in the chlorpheniramine/pseudoephedrine group. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| loratadine 5 mg and pseudoephedrine 120 mg BID<br><br>Products were ER fixed-dose combinations. | | | | Reduction in mean total nasal and non-nasal symptom scores was comparable between the two treatment groups. By day 14, nasal symptom improvement was 60% in the loratadine/pseudoephedrine group and 61% in the chlorpheniramine/pseudoephedrine group. Improvement was comparable for nasal discharge (53 vs 45%, respectively), stuffiness (52 vs 44%, respectively), and sneezing (61 vs 54%, respectively) on day three.<br><br>Improvement in mean total non-nasal symptom scores was comparable and not significantly different between the two treatment groups on day three (P value not reported). At day 14, improvement in non-nasal symptom scores was 69% in both study groups. Patients in the chlorpheniramine/pseudoephedrine group showed greater relief of red eyes at day three (63 vs 54%) and day 14 (75 vs 68%). Patients treated with loratadine/pseudoephedrine showed greater improvement in ear/palate itch (60 vs 50%) at day 14.<br><br>The most frequently reported side effects were headache (16% in both groups) and insomnia (16% in the loratadine/pseudoephedrine group and 18% in the chlorpheniramine/pseudoephedrine group). There was a greater incidence of fatigue (6 vs 25%, P<0.01), dry mouth (7 vs 19%; P=0.07), and sedation (7 vs 22%; P<0.03) in the group receiving chlorpheniramine/pseudoephedrine compared to those receiving loratadine/pseudoephedrine.<br><br>Secondary:<br>Not reported |
| Gibbs et al.[37] (1998)<br><br><u>Study 2</u><br>Clemastine 1.34 mg TID for 5 days<br><br>vs<br><br>acrivastine 8 mg | RCT, XO<br><br>Adults with seasonal allergic rhinitis | N=54<br><br>21 days | Primary:<br>Nasal and non-nasal symptoms<br><br>Secondary:<br>Not reported | Primary:<br>*Study 2*<br>The acrivastine was significantly better than placebo for the relief of itchy nose, blocked nose and watery eyes symptoms, and for calculated overall symptom score (mean of all seven symptoms). Clemastine was significantly better than placebo for alleviation of the symptoms of itchy nose, running nose, itchy eyes and watery eyes, and for calculated overall symptom score. There were no significant differences between the two antihistamines. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| TID for 5 days<br><br>vs<br><br>placebo for 5 days<br><br><u>Study 1</u><br>Acrivastine 4 mg TID for 5 days<br><br>vs<br><br>acrivastine 8 mg TID for 5 days<br><br>vs<br><br>placebo for 5 days | | | | In study 2, drowsiness was reported by seven (39%) patients receiving clemastine compared to one patient receiving acrivastine (P<0.05).<br><br>*Study 1*<br>High- and low-dose acrivastine led to significantly lower scores than placebo for all symptoms, except blocked nose (P>0.01). There was no significant difference in symptom scores between the two doses of acrivastine.<br><br>Sixty-three percent of patients rated symptom control as excellent or good during treatment with 8 mg acrivastine compared with 46% for 4 mg acrivastine and 36% for placebo (8 mg acrivastine vs placebo; P=0.058).<br><br>There were no statistically significant differences in the proportion of patients who would have requested further treatment had it been available on prescription although slightly more patients on 4 mg acrivastine (61%) and 8 mg acrivastine (62%) than on placebo (54%) indicated this desire. Only 20% of patients preferred treatment with placebo. This is compared to 40% of patients preferring acrivastine 4 mg and 40% preferring acrivastine 8 mg.<br><br>Secondary:<br>Not reported |
| Sheriff et al.[38] (1976)<br><br>Clemastine 1.34 mg given as 1 to 2 tablets 2 to 3 times daily<br><br>vs<br><br>chlorpheniramine 4 mg given as 1 to 2 tablets 2 to 3 times daily | DB, PG, RCT<br><br>Patients 7 to 40 years of age with seasonal allergic rhinitis | N=51<br><br>2 weeks | Primary:<br>Mean total number of tablets taken, mean TSSs, mean number of days the patient felt drowsy, investigator's and patient's assessment of effectiveness of treatment<br><br>Secondary:<br>Not reported | Primary:<br>The mean number of tablets taken was similar with clemastine (27.8) and chlorpheniramine (28.1; P value not significant).<br><br>The mean TSSs were similar with clemastine (16.2) and chlorpheniramine (14.0; P value not significant).<br><br>The mean number of days drowsy was similar with clemastine (1.58) and chlorpheniramine (1.08; P value not significant).<br><br>The effectiveness of clemastine and chlorpheniramine as defined by the investigator's assessments and by the patients' daily record forms were similar among the two treatment groups. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Secondary:<br>Not reported |
| Thomas et al.[39] (1977)<br><br>Clemastine 2.68 mg as a single dose<br><br>vs<br><br>chlorpheniramine 4 mg as a single dose<br><br>vs<br><br>placebo | DB, RCT<br><br>Patients >15 years of age with seasonal allergic rhinitis | N=46<br><br>1 day | Primary:<br>Alteration in airway resistance, nasal congestion, nasal obstruction, nasal airway patency, investigator's and patient's subjective assessments of improvement<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with clemastine and chlorpheniramine resulted in significant changes in the plethysmographic oral resistance evaluations compared to baseline. There were no significant differences noted with placebo compared to baseline. Clemastine was significantly better than placebo for hours two and six (P<0.10) and for the mean response over all time points (P<0.05). There were no significant differences for patients receiving chlorpheniramine compared to placebo.<br><br>Differences in nasal resistance and total airway resistance among the three treatment groups were not significant.<br><br>Treatment with clemastine and chlorpheniramine resulted in significant improvements in nasal congestion compared to baseline. Both clemastine and chlorpheniramine also demonstrated greater improvements in nasal congestion compared to placebo at all time points and overall (P<0.05).<br><br>There were no significant differences in nasal obstruction among the three treatment groups.<br><br>Treatment with clemastine and chlorpheniramine led to improvements in the investigator's subjective evaluation of nasal congestion at each time point. There was no difference noted with placebo. More patients treated with clemastine showed improvement (64 to 73%) compared to placebo (9 to 18%; P<0.05). There was no significant difference in nasal congestion with chlorpheniramine compared to placebo.<br><br>There were no significant differences in the overall improvement index of physician-evaluated signs among the three treatment groups.<br><br>Patients' self-evaluation of changes in symptoms showed improvement in all treatment groups.<br><br>The most common adverse reaction was drowsiness. The number of patients with severe drowsiness was higher in the chlorpheniramine group |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | than in the placebo group (P<0.10).<br><br>Secondary:<br>Not reported |
| Todd et al.[40] (1975)<br><br>Study 1<br>Clemastine 1.34 mg BID to QID<br><br>vs<br><br>chlorpheniramine 4 mg BID to QID<br><br>Study 2<br>Clemastine elixir 0.5 mg BID<br><br>vs<br><br>chlorpheniramine syrup 2 mg BID | DB, PG, RCT<br><br>Study 1<br>Adults with allergic rhinitis<br><br>Study 2<br>Children with allergic rhinitis | Study 1<br>N=58<br><br>3 weeks<br><br>Study 2<br>N=42<br><br>3 weeks | Primary:<br>Physician's assessment of improvement after treatment<br><br>Secondary:<br>Not reported | Primary:<br>*Study 1*<br>In the physician's assessment of improvement, 50% of clemastine-treated patients were to be greatly improved compared to 23% (improved), 13% (no change), and 13% (worse). This is compared to 28% of patients in the chlorpheniramine group who were considered to be greatly improved, 43% (improved), 14% (no change), and 14% (worse). There were no P values reported.<br><br>Adverse events were minimal with both preparations. Drowsiness when reported was mainly of a transient nature with no significant difference in incidence or severity between the compounds.<br><br>*Study 2*<br>In the physician's assessment of improvement, 32% of clemastine-treated patients were to be greatly improved compared to 21% (improved), 11% (no change), and 32% (worse). This is compared to 31% of patients in the chlorpheniramine group who were considered to be greatly improved, 13% (improved), 4% (no change), and 52% (worse). There were no P values reported.<br><br>There were no reports of drowsiness or tiredness from any of the 19 patients receiving clemastine. Of the 23 patients receiving chlorpheniramine, three complained of drowsiness.<br><br>Secondary:<br>Not reported |
| Dockhorn et al.[41] (1987)<br><br>Clemastine 1.34 mg BID | DB, MC, PC, PG, RCT<br><br>Patients with seasonal allergic rhinitis | N=330<br><br>14 days | Primary:<br>Assessment of nasal and non-nasal symptoms, overall condition or rhinitis, and | Primary:<br>Improvement in mean total symptoms scores and nasal symptom scores were significantly greater with loratadine and clemastine than placebo at each time point (P<0.01). There was no significant difference between the loratadine and clemastine treatment groups (P value not significant) at day three, day 14, or study end point. At day seven, the improvement in the |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>loratadine 10 mg QD<br><br>vs<br><br>placebo | | | therapeutic response to treatment<br><br>Secondary:<br>Not reported | loratadine group was significantly greater than that of the clemastine group (P=0.04 for TSSs and P=0.05 for nasal symptom scores). Non-nasal symptom scores were not reported.<br><br>In the physician evaluation of therapeutic response, loratadine and clemastine led to a more favorable response to treatment than placebo. By day three, an excellent response was seen in 22% of loratadine-treated patients, 9% of the clemastine-treated patients, and 3% of the placebo-treated patients. Likewise, 22, 43, and 23%, respectively, were rated as have a good response to treatment. In the end point analysis, the percentage of patients with a good or excellent response to treatment was 29 and 27%, respectively with loratadine; 13 and 42%, respectively with clemastine; 5 and 27%, respectively with placebo.<br><br>A greater percentage of patients reported at least one adverse event with clemastine (37%) than with loratadine (21%) or placebo (20%; P<0.01). Sedation was reported by a greater percentage of patients receiving clemastine (22%) than loratadine (6%) or placebo (5%; P<0.01). There was no difference in dry mouth among the treatment groups.<br><br>Secondary:<br>Not reported |
| Frølund et al.[42] (1990)<br><br>Clemastine 1.34 mg BID<br><br>vs<br><br>loratadine 10 mg QD<br><br>vs<br><br>placebo | DB, MC, PG, RCT<br><br>Patients 18 to 65 years of age with perennial allergic rhinitis | N=155<br><br>3 weeks | Primary:<br>Total, nasal and non-nasal symptom severity<br><br>Secondary:<br>Not reported | Primary:<br>The loratadine and clemastine groups showed a significant improvement compared to placebo when nasal membranes, secretion, and patency were assessed with rhinoscopy (P<0.05).<br><br>Loratadine and clemastine significantly reduced patients' total nasal and total eye symptoms compared to placebo (P<0.05). A similar reduction was seen for all four nasal symptoms (discharge, stuffiness, itching, and sneezing). For eye symptoms, this decrease was found for redness and itching (P<0.05), but no significant decrease was observed for tearing.<br><br>Loratadine improved total symptoms scores at day seven compared to clemastine (P<0.05). Loratadine also improved nasal itching and nasal stuffiness more effectively than clemastine at day seven (P<0.05). There were no significant changes between the treatment groups at other time |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | points.<br><br>The diary cards showed there was a significant onset of relief of symptoms within the first day of treatment with loratadine and clemastine compared to placebo. A faster onset of symptom relief was also seen in the loratadine group compared with the clemastine group within the first day (P<0.05).<br><br>There were fewer adverse events reported with loratadine compared to clemastine (P<0.05) and placebo (P<0.05).<br><br>Secondary:<br>Not reported |
| Irander et al.[43] (1990)<br><br>Clemastine 1.34 mg BID<br><br>vs<br><br>loratadine 40 mg QD<br><br>vs<br><br>placebo | DB, RCT<br><br>Patients >18 years of age with a history of rhino-conjunctivitis during the birch pollen season | N=107<br><br>2 weeks | Primary:<br>Rhino-conjunctivitis symptoms<br><br>Secondary:<br>Not reported | Primary:<br>Loratadine significantly reduced all rhino-conjunctivitis symptoms compared to placebo, except for nasal stuffiness (P value not significant).<br><br>Clemastine significantly reduced sneezing, nasal discharge, and tearing compared to placebo; however, there was no difference in nasal itching/stuffiness, ocular itching/redness, or palatal itching (P value not significant).<br><br>There was no significant difference in the majority of the rhino-conjunctivitis symptoms between clemastine and loratadine, except for ocular itching/redness (P<0.05).<br><br>Sedation was the most common adverse event. There was no difference in sedation with loratadine compared to placebo; however, a significantly higher incidence was noted in patients treated with clemastine (P<0.05). Dizziness, headache, insomnia, dryness of the mouth and nausea were reported rarely.<br><br>Secondary:<br>Not reported |
| Boner et al.[44] (1989) | RCT<br><br>Children 4 to 12 | N=40<br><br>14 days | Primary:<br>Symptom severity | Primary:<br>Symptom severity (on physical exam and subjective symptoms) improved with both drugs during the 14-day treatment period (P<0.01). There was |

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| Dex-chlorpheniramine 1 mg every 8 hours<br><br>vs<br><br>loratadine 5 mg QD<br><br>Children under 6 years and those weighing less than 20 kg received half the dose. | years of age with moderate-to-severe seasonal allergic rhinitis | | Secondary:<br>Not reported | no significant difference between the dexchlorpheniramine or loratadine treatment groups (P=0.295).<br><br>Rhinoscopy showed a reduction in nasal secretions/stuffiness with both treatments and there was no significant difference between the treatment groups (P value not significant).<br><br>The evaluation of therapeutic results by both the investigator and the patient/parent had similar positive results with both drugs at each visit (P>0.05).<br><br>Four children receiving dexchlorpheniramine had somnolence on day one, two other patients complained of mild epistaxis during the first three days of treatment. Two children in the loratadine group had two episodes of moderate epistaxis, one on days one to two and the other on days six to eight, no child reported drowsiness.<br><br>Secondary:<br>Not reported |
| Raphael et al.[45] (2006)<br><br>Diphenhydramine 50 mg TID<br><br>vs<br><br>desloratadine 5 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients 12 to 65 years of age with moderate-to-severe seasonal allergic rhinitis | N=610<br><br>1 week | Primary:<br>Change from baseline in the TNSS<br><br>Secondary:<br>Change from baseline in TSS, individual symptom scores, global evaluation of response to treatment | Primary:<br>Diphenhydramine had a 46.7% greater reduction in patient TNSSs compared with desloratadine (-1.81; P<0.001). Investigator TNSS results were similar to those recorded by patients.<br><br>Secondary:<br>Diphenhydramine had a 45.5% greater reduction in patient TSS compared with desloratadine (-3.35; P<0.001). Investigator TSS results were similar to those recorded by patients.<br><br>Treatment with diphenhydramine led to significant reductions in all eight individual symptom scores compared to placebo and desloratadine, including nasal congestion. Treatment with desloratadine led to a greater reduction in six of the eight individual symptoms compared to placebo (nasal congestion, rhinorrhea, sneezing, nasal itching, redness of eyes, and itching ears/palate); however, only sneezing was significant (-027; P=0.04). Similar results were observed for investigator-scored individual symptoms. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | The daily nasal congestion scores were significantly reduced with diphenhydramine compared to desloratadine and placebo throughout the seven-day treatment period.<br><br>Percentage improvement in the patient mean global response to treatment scores over placebo were 134.5% (P<0.001) for diphenhydramine and 29.4% (P=0.20) for desloratadine. Diphenhydramine had an 81.2% (P<0.001) greater improvement in the patient mean global response to treatment score compared with desloratadine.<br><br>Adverse events were observed in 35.3, 16.3, and 8.3% of patients who received diphenhydramine, desloratadine, and placebo, respectively. The most common adverse events were somnolence, dry mouth, asthenia, headache, and dizziness. |
| Park et al.[46] (2011)<br><br>Diphenhydramine 1 mg/kg<br><br>vs<br><br>cetirizine 0.25 mg/kg | DB, RCT<br><br>Patients 3 to 19 years of age experiencing an allergic reaction during oral food challenge | N=64<br>70 allergic reactions<br><br>Duration not specified | Primary:<br>Proportion of patients experiencing sedation (sedation score of 1 or 2)<br><br>Secondary:<br>Mean resolution of urticaria and pruritus, administration of other medications | Primary:<br>Overall, 28.6 and 17.1% of patients receiving diphenhydramine and cetirizine experienced sedation, reflecting a nonsignificant difference in sedation of 11.4% (95% CI, -8.4 to 30.2%).<br><br>Secondary:<br>The mean time to resolution of urticaria and pruritus was similar between the two treatments. Among patients receiving diphenhydramine, mean time to resolution was 42.3±13.15 minutes compared to 40.8±22.11 minutes among patients receiving cetirizine (P=0.86). For pruritus the corresponding times were 28.6±20.54 and 31.3±20.07 minutes (P=0.67). Furthermore, the mean time to first onset of resolution of urticaria and pruritis was similar between the two treatments.<br><br>There was no difference in the administration of other medications between the two treatments. Other treatments included steroid and/or epinephrine. |
| Connell et al.[47] (1982)<br><br>Triprolidine 2.5 mg and | DB, PC, RCT<br><br>Patients >16 years of age with seasonal allergic rhinitis | N=184<br><br>2 days | Primary:<br>TARs, nasal congestion scores, hay fever symptom complex score, | Primary:<br>There was no difference in the mean TARs among the four treatment groups. Triprolidine/pseudoephedrine was better than triprolidine (P≤0.025) at 12.30 hours, 13.30 hours and 15.30 hours (borderline) on Day 1, and at 15.30 hours on Day 2. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| pseudoephedrine 60 mg given every 6 hours as a fixed-dose combination<br><br>vs<br><br>triprolidine 2.5 mg given every 6 hours<br><br>vs<br><br>pseudoephedrine 60 mg given every 6 hours<br><br>vs<br><br>placebo | | | patient's perception of overall therapeutic benefit<br><br>Secondary:<br>Not reported | For the end point of mean nasal congestion scores vs hour after dosing, triprolidine/pseudoephedrine was better (P≤0.025) than: (1) triprolidine at 13.30 hours and 15.30 hours on Day 2; and (2) placebo at 10.30 hours, 11.30 hours (borderline), 12.30 hours (borderline), 13.30 hours (borderline), 14.30 hours, 15.30 hours (borderline), and 16.30 hours on Day 2.<br><br>For the end point of hay fever symptom complex score, triprolidine/pseudoephedrine was better (P≤0.025) than: (1) pseudoephedrine at 12.30-14.30 hours, and 16.30 hours on Day 1, and at 13.30 hours (borderline), 15.30 and 16.30 hours on Day 2; and (2) placebo at 12.30-14.30 hours, and 15.30 hours (borderline) on Day 1, and at 08.30 hours, 10.30-11.30 hours (borderline) and 12.30-16.30 hours on Day 2. The mean symptom complex score was also better with triprolidine/pseudoephedrine compared to pseudoephedrine and placebo (P=0.01, respectively).<br><br>The patients' perception of overall therapeutic benefit was assessed at 08.30 hours on Day 2 by the question "Did the medication help?" For patients receiving triprolidine/pseudoephedrine, 52% said they noticed marked improvement compared to those receiving triprolidine (22%), pseudoephedrine (17%), or placebo (9%).<br><br>The three most frequently reported adverse events were dry nose, drowsiness and headache.<br><br>Secondary:<br>Not reported |
| Diamond et al.[48] (1981)<br><br>Triprolidine 2.5 mg and pseudoephedrine 60 mg as a fixed-dose combination | DB, PC, RCT<br><br>Patients >18 years of age with seasonal allergic rhinitis | N=151<br><br>1 day | Primary:<br>NAR, symptom complex score, nasal congestion score, adverse events<br><br>Secondary: | Primary:<br>Treatment with triprolidine/pseudoephedrine resulted in a greater reduction in NAR compared to triprolidine at all time points after one hour (P≤0.025) and a greater reduction in NAR compared to placebo at hours six and seven (P≤0.025). There was no statistical comparison with pseudoephedrine alone for this end point. When the area under the NAR-time curves were compared, the overall response to treatment was greater with triprolidine/pseudoephedrine than triprolidine or placebo (P≤0.025). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| given at 10:00 AM, 1:00 PM, and 4:00 PM (3 doses)<br><br>vs<br><br>triprolidine 2.5 mg given at 10:00 AM, 1:00 PM, and 4:00 PM (3 doses)<br><br>vs<br><br>pseudoephedrine 60 mg given 10:00 AM, 1:00 PM, and 4:00 PM (3 doses)<br><br>vs<br><br>placebo | | | Not reported | Reduction in the nasal congestion scores were greater with triprolidine/pseudoephedrine compared to placebo (hours six, seven and eight; P≤0.025) and triprolidine (hours six and eight; P≤0.025). There was no difference in nasal congestion scores between triprolidine/pseudoephedrine and pseudoephedrine alone.<br><br>For the end point of symptom complex scores, triprolidine/ pseudoephedrine resulted in a greater reduction in symptoms compared to pseudoephedrine alone at hours three, six, seven and eight and a greater reduction in symptoms compared to placebo at hours three, four, six, seven and eight (P≤0.025, respectively). The mean symptom complex score was also better with triprolidine/pseudoephedrine compared to pseudoephedrine and placebo (P≤0.025, respectively). There was no difference in symptom complex scores between triprolidine/pseudoephedrine and triprolidine alone.<br><br>Drowsiness was the most frequently reported adverse event.<br><br>Secondary:<br>Not reported |
| Empey et al.[49] (1975)<br><br>Triprolidine 2.5 mg and pseudoephedrine 60 mg TID for 2 weeks<br><br>vs<br><br>triprolidine 2.5 mg TID for 2 weeks<br><br>vs | DB, PC, XO<br><br>Adults with seasonal allergic rhinitis | N=40<br><br>10 weeks | Primary:<br>Symptoms (daily diary card), patient's overall impression of improvement, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>The mean number of days sneezing occurred was lower with triprolidine/pseudoephedrine (4.05 days) compared to triprolidine (6.1 days), pseudoephedrine (6.53 days) and placebo (7.33 days; P<0.05 for all comparisons). Triprolidine/pseudoephedrine was also more effective than pseudoephedrine and placebo in reducing the severity of sneezing (P<0.05). There was no difference in severity of sneezing between triprolidine/pseudoephedrine and triprolidine alone.<br><br>The three active treatment groups were more effective than placebo in reducing the number of days of rhinorrhea and eye irritation occurred, as well as the severity of these symptoms (P<0.05 for all comparisons with placebo). There were no significant differences noted among the three active treatment groups.<br><br>There was no significant difference in the number of days of nasal |

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| pseudoephedrine TID for 2 weeks<br><br>vs<br><br>placebo for 2 weeks | | | | blockage, or the severity of this symptom, among the 4 treatment groups.<br><br>Overall scores on the "better or worse than usual" assessment and the patient's choices of "best or joint best period" showed triprolidine/pseudoephedrine was preferred to triprolidine alone, pseudoephedrine alone, or placebo.<br><br>Drowsiness, dry mouth and dizziness were the most commonly reported adverse events.<br><br>Secondary:<br>Not reported |
| **Urticaria** | | | | |
| Jolliffe et al.[50] (1985)<br><br>Brompheniramine SR 12 mg BID for 4 weeks<br><br>vs<br><br>clemastine 1 mg BID for 4 weeks<br><br>vs<br><br>placebo for 4 weeks | PC, XO<br><br>Patients 18 to 62 years of age with chronic urticaria (with or without dermatographism) | N=24<br><br>12 weeks | Primary:<br>Symptom severity and degree of improvement<br><br>Secondary:<br>Not reported | Primary:<br>Investigators and patients found that both brompheniramine and clemastine were more effective than placebo with regards to symptom severity.<br><br>In those patients who expressed a positive preference for one therapy, more patients preferred brompheniramine treatment to either clemastine (P<0.025) or placebo treatment (P<0.005).<br><br>Drowsiness was experienced by four patients taking brompheniramine compared to three patients taking clemastine.<br><br>Secondary:<br>Not reported |
| Gale et al.[51] (1989)<br><br>Chlorpheniramine 4 mg TID for 24 days<br><br>vs | DB, RCT, XO<br><br>Patients >16 years of age with chronic idiopathic urticaria | N=20<br><br>48 days | Primary:<br>Patients' and physician's assessment of treatment of chronic idiopathic urticaria | Primary:<br>There were no significant differences between acrivastine and chlorpheniramine in relieving itching, wheal, or overall discomfort in the patient assessment (P value not reported).<br><br>There were no significant differences between acrivastine and chlorpheniramine in itching or wheal in the physician's assessment (P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| acrivastine<br>8 mg TID for 24 days | | | Secondary:<br>Not reported | Secondary:<br>Not reported |
| **Upper Respiratory Conditions** | | | | |
| Bye et al.[52]<br>(1980)<br><br>Triprolidine 2.5 mg and pseudoephedrine 60 mg 1 tablet TID<br><br>vs<br><br>triprolidine 2.5 mg 1 tablet TID<br><br>vs<br><br>pseudoephedrine 60 mg 1 tablet TID<br><br>vs<br><br>placebo<br><br>Tablets were taken for as long as needed. | DB, PC, RCT<br><br>Adults with symptoms of the common cold | N=466<br>(243 colds)<br><br>8 to 10 days | Primary:<br>Symptoms (daily diary card), adverse events, overall impression of improvement<br><br>Secondary:<br>Not reported | Primary:<br>The sneezing score was reduced with triprolidine/pseudoephedrine compared to placebo on days two, three and four of the cold (P<0.01). Sneezing was also reduced by pseudoephedrine on days two and three compared to placebo (P<0.01).<br><br>Nasal obstruction was improved with pseudoephedrine and triprolidine/pseudoephedrine on day one only (P<0.01).<br><br>The other specific symptoms were not significantly affected by the treatments.<br><br>Difficulty in sleeping was significantly higher for patients taking pseudoephedrine compared to placebo.<br><br>Significantly more patients receiving pseudoephedrine and triprolidine/pseudoephedrine reported “improvement” improved in symptoms compared to placebo (P<0.01).<br><br>Secondary:<br>Not reported |
| **Central Nervous System Adverse Effects** | | | | |
| Seppälä et al.[53]<br>(1981)<br><br>Brompheniramine 12 mg for 3 doses | DB, RCT, XO<br><br>Health men 20 to 25 years of age | N=9<br><br>5 weeks | Primary:<br>Psychomotor performance, subjective assessments, sleep estimates | Primary:<br>No significant drug effects were seen on divided attention, tracking or on the speed anticipation test.<br><br>The reaction times quickened during the study (P<0.01). The reactions of the subjects were slower (P<0.05 vs placebo) two hours after the first dose |

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| vs<br><br>carbinoxamine 12 mg for 3 doses<br><br>vs<br><br>clemastine 1.34 mg for 3 doses<br><br>vs<br><br>phenyl-propanolamine 50 mg for 3 doses<br><br>vs<br><br>placebo<br><br>Doses were administered at 8:30 AM and 9:00 PM on the first day, and at 8:30 AM on the following day. | | | Secondary:<br>Not reported | of carbinoxamine on day one, but reactions returned to normal thereafter. Phenylpropanolamine improved reaction times (P<0.05) compared to placebo, carbinoxamine and brompheniramine.<br><br>Clemastine and brompheniramine slightly decreased and phenylpropanolamine significantly decreased (P<0.001) reaction mistakes compared to placebo.<br><br>On both treatment days, phenylpropanolamine enhanced the ability to distinguish between two discrete flashes of light. The effect was significant in comparison with placebo, carbinoxamine and brompheniramine (P<0.01).<br><br>No treatment significantly affected the subjective feeling of performance. On the first day of treatment, antihistamines were estimated to be a tranquilizer more often than placebo, but only clemastine differed significantly from placebo (P<0.05). On day two, no active treatment differed from placebo.<br><br>Diurnal variation in the alertness-drowsiness scale was seen during placebo administration. Antihistamines tended to cause drowsiness. Significant differences in drowsiness were seen with brompheniramine (six hours after dose) and clemastine (12 hours after dose) compared to placebo. Drowsiness was felt only on the first day of antihistamine treatment. Phenylpropanolamine increased alertness.<br><br>Secondary:<br>Not reported |
| Nicholson et al.[54] (1979)<br><br>Brompheniramine 4 mg IR as a single dose<br><br>vs | DB, PC, RCT, XO<br><br>Healthy volunteers | N=6<br><br>>4 weeks | Primary:<br>Visuomotor coordination and subjective assessments of performance, well-being and sleep<br><br>Secondary: | Primary:<br>Brompheniramine IR (4 mg) impaired performance at 1.5 hours and 3.0 hours (P<0.05). Brompheniramine SR (12 mg) impaired performance at 1.5 hours (P<0.001).<br><br>Triprolidine IR (2.5 mg) had an immediate effect on performance (P<0.001) which persisted for 3.0 hours (P<0.01). Triprolidine SR (10 mg) impaired performance from 1.5 hours (P<0.001) to 5.0 hours (P<0.01). |

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| brompheniramine 12 mg SR as a single dose<br><br>vs<br><br>triprolidine 2.5 mg IR as a single dose<br><br>vs<br><br>triprolidine 10 mg SR as a single dose<br><br>vs<br><br>placebo | | | Not reported | Performance reached placebo level about seven hours after triprolidine (2.5 and 10 mg), and about five hours after brompheniramine (4 and 12 mg).<br><br>There were no consistent changes in the assessments of well-being, sleep and performance among any of the antihistamines compared to placebo.<br><br>Secondary:<br>Not reported |
| Ng et al.[55] (2004)<br><br>Chlorpheniramine 4 mg as a single dose<br><br>vs<br><br>cetirizine 10 mg as a single dose<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Children 7 to 14 years of age with allergic rhinitis | N=24<br><br>>3 weeks | Primary:<br>P300 event-related potential (objective measure of sedation) and sleepiness or somnolence using a VAS (subjective measure of sedation)<br><br>Secondary:<br>Not reported | Primary:<br>There was an increase in P300 latency for chlorpheniramine (P=0.04) and cetirizine (P=0.03) compared to baseline, but this was not demonstrated with placebo. However, the mean percentage change in P300 latency for cetirizine and chlorpheniramine did not differ significantly from placebo.<br><br>There was no significant increase in VAS scores for chlorpheniramine, cetirizine or placebo compared to baseline (P>0.05). The mean percentage change in VAS scores for cetirizine and chlorpheniramine did not differ significantly from placebo.<br><br>Secondary:<br>Not reported |
| Kamei et al.[56] (2003)<br><br>Chlorpheniramine 4 mg as a single | DB, PC, RCT, XO<br><br>Healthy volunteers | N=11<br><br>4 weeks | Primary:<br>CFF, CRT, CTT, RVIP, LARS, WA<br><br>Secondary: | Primary:<br>There was no significant difference in CFF or CRT among the treatment groups.<br><br>Chlorpheniramine significantly reduced the tracking ability in the CTT |

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| dose<br><br>vs<br><br>fexofenadine 120 mg as a single dose<br><br>vs<br><br>olopatadine 10 mg as a single dose<br><br>vs<br><br>placebo | | | Not reported | compared to placebo (P<0.01).<br><br>There was no significant difference in RVIP among the treatment groups.<br><br>There was no significant difference in LARS among the treatment groups.<br><br>In the WA analysis, chlorpheniramine and olopatadine caused a significant reduction in behavioral activity compared to placebo (P<0.05 and P<0.01, respectively). There was also a significant difference between fexofenadine and olopatadine groups (P<0.01).<br><br>Secondary:<br>Not reported |
| Hindmarch et al.[57] (1976)<br><br>Clemastine 1.34 mg BID for 3 days<br><br>vs<br><br>placebo | DB, PC, XO<br><br>Healthy volunteers | N=21<br><br>11 days | Primary:<br>Car driving ability, personality and subjective feeling states<br><br>Secondary:<br>Not reported | Primary:<br>There was no significant difference in car driving ability (garaging a car, controlled braking ability, estimation of width at a distance, maneuvering ability, reverse parking) with clemastine compared to placebo.<br><br>There was no significant difference in the Middlesex Hospital Questionnaire between clemastine and placebo, which assessed personality and subjective feeling states.<br><br>Secondary:<br>Not reported |
| Cohen et al.[58] (1987)<br><br><u>Study 1</u><br>Diphenhydramine 50 mg<br><br>vs<br><br>diphenhydramine | DB, PC, XO<br><br>Healthy volunteers | <u>Study 1</u><br>N=12<br><br>Single dose<br><br><u>Study 2</u><br>N=12<br><br>Single dose | Primary:<br>Adaptive tracking test, reaction time, body sway, eye movement tests (Study 1)<br><br>Secondary:<br>Not reported | Primary:<br>*Study 1*<br>Alcohol alone and acrivastine alone produced no impairment in tracking performance at any time during the study. Diphenhydramine alone (50 mg) reduced tracking performance at 2.5 hours after drug administration compared to placebo. At one hour, the effects of diphenhydramine plus alcohol were significantly different from placebo, but not from alcohol alone. At 2.5 hours, diphenhydramine plus alcohol (50 mg) caused impairment of performance compared to all other treatment groups. Acrivastine plus alcohol (8 mg) impaired tracking at 2.5 hours compared |

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| 50 mg and alcohol 32 mL<br><br>vs<br><br>acrivastine 8 mg<br><br>vs<br><br>acrivastine 8 mg and alcohol 32 ml<br><br>vs<br><br>alcohol 32 ml<br><br>vs<br><br>placebo<br><br><u>Study 2</u><br>Acrivastine 4 mg and alcohol 32 mL<br><br>vs<br><br>acrivastine 8 mg and alcohol 32 mL<br><br>vs<br><br>terfenadine† 60 mg and alcohol 32 mL<br><br>vs<br><br>terfenadine† 120 | | | | with placebo and single treatments, but produced significantly less impairment than diphenhydramine plus alcohol (50 mg).<br><br>No single treatment prolonged reaction time at any time, with the exception of alcohol alone. It significantly increased reaction time compared to placebo at one hour. At one hour, diphenhydramine plus alcohol (50 mg) increased reaction time compared to placebo and all other treatments. At 2.5 hours, diphenhydramine plus alcohol (50 mg) was different from all of the single treatments (including placebo), but did not differ from the acrivastine and alcohol (8 mg) combination. The acrivastine plus alcohol (8 mg) differed from placebo and acrivastine alone at one hour, but not from alcohol alone. At 2.5 hours, acrivastine plus alcohol (8 mg) prolonged reaction time compared with placebo, alcohol and acrivastine alone.<br><br>With regards to body sway, the main effects occurred at one hour. Impairment after the diphenhydramine plus alcohol (50 mg) combination was significantly different from all single treatments (excluding diphenhydramine alone). The acrivastine plus alcohol (8 mg) combination differed from placebo, alcohol alone and acrivastine alone.<br><br>The eye movement analyses included smooth pursuit velocity, as well as PSV duration and reaction time. Diphenhydramine plus alcohol (50 mg) impaired PSV compared with placebo and alcohol at 1 and 2.5 hour(s). At 2.5 and 7.5 hours, PSV was also decreased by diphenhydramine alone (50 mg). No significant differences were seen after acrivastine (8 mg) or alcohol, either alone or in combination. The duration of the saccades of 30° showed similar effects to the PSV. Diphenhydramine plus alcohol (50 mg) was different from placebo, alcohol alone, and acrivastine alone (8 mg) at one hour and from all the other treatments at 2.5 hours. At 2.5 hours, diphenhydramine alone (50 mg) was different from placebo. Both acrivastine (8 mg) and alcohol alone produced no effects, but their combination increased the duration of saccade at 1 and 2.5 hour(s) compared with placebo, but not with alcohol alone. Diphenhydramine alone (50 mg) and the combination with alcohol produced prolongation in the duration of saccade at 1 and 2.5 hour(s) compared with placebo. At 2.5 hours, diphenhydramine plus alcohol (50 mg) also produced significant |

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| mg and alcohol 32 mL<br><br>vs<br><br>alcohol 32 mL<br><br>vs<br><br>placebo | | | | impairment compared to alcohol alone. None of the other single treatments produced impairment compared with placebo. Acrivastine plus alcohol (8 mg) impaired reaction time at 1 and 2.5 hour(s) compared with placebo, but not with alcohol. Smooth pursuit velocity was significantly reduced after alcohol and acrivastine plus alcohol (8 mg) compared with placebo, but acrivastine plus alcohol (8 mg) was not different from alcohol alone. There were no differences between placebo and any of the other treatments.<br><br>*Study 2*<br>At 1 hour, alcohol alone and all drug/alcohol combinations prolonged reaction time and there were no differences between the combination treatments and alcohol alone. At 2.5 hours, the combination treatments had prolonged reaction time compared with placebo, but alcohol did not. There were no differences between alcohol-containing treatments and alcohol alone.<br><br>With regards to body sway, at 1 and 2.5 hour(s), all drug/alcohol combinations and alcohol alone differed significantly from placebo. However, there was no difference between any of the active treatments.<br><br>Secondary:<br>Not reported |
| Ramaekers et al.[59] (1994)<br><br>Diphenhydramine-50 mg as a single dose<br><br>vs<br><br>acrivastine 8 mg as a single dose<br><br>vs | DB, RCT, XO<br><br>Healthy female volunteers 21 to 45 years of age | N=18<br><br>10 to 11 weeks | Primary:<br>Two repetitions of the highway driving test and car-following test given 1.5 to 2.75 hours (first trial) and 3.25 to 4.50 hours (second trial) post dosing<br><br>Secondary:<br>Not reported | Primary:<br>*Highway Driving*<br>All acrivastine doses significantly impaired driving (P<0.05) in the first trial. Only the 24 mg dose remained significant in the second trial (P=0.014). The combination of acrivastine (8 mg) with pseudoephedrine (60 mg) had no significant effect on highway driving in either trial. There was no significant effect of any terfenadine dose in either trial. Diphenhydramine significantly impaired driving in both trials (P=0.000 and 0.001, respectively).<br><br>The effect of diphenhydramine differed from all other treatments in both trials, except acrivastine 16 and 24 mg. In the first trial, the effect of 16 mg acrivastine differed significantly from that of all three terfenadine doses. In the second trial, the effect of 24 mg acrivastine differed |

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| acrivastine 16 mg as a single dose<br><br>vs<br><br>acrivastine 24 mg as a single dose<br><br>vs<br><br>acrivastine 8 mg and pseudoephedrine 60 mg as a single dose<br><br>vs<br><br>terfenadine 60 mg as a single dose<br><br>vs<br><br>terfenadine 120 mg as a single dose<br><br>vs<br><br>terfenadine 180 mg as a single dose<br><br>vs<br><br>placebo | | | | significantly from that of terfenadine (120 and 60 mg). No other pair of treatment effects differed significantly.<br><br>The difference in driving impairment was significant between placebo and diphenhydramine in both trials (P=0.010 and P=0.020, respectively); between placebo and acrivastine (16 mg) and terfenadine (60 mg) in the first trial (P=0.001 and P=0.031, respectively); between placebo and acrivastine (24 mg) in the second trial (P=0.018). The combination of acrivastine and pseudoephedrine had no significant effect on driving impairment compared to placebo.<br><br>*Car-Following Test*<br>The combined effect of all acrivastine doses on reaction time was significant in the first trial (P=0.046). The effects were also significant specifically for the 16 mg dose (P=0.027) and the 24 mg dose (P=0.04) compared to placebo. The effect of 24 mg dose remained significant in the second trial (P=0.025). The combination of acrivastine with pseudoephedrine had no significant effect on reaction time in either trial compared to placebo. There was no significant effect of any terfenadine dose (or combination of doses) in either trial. Diphenhydramine significantly affected reaction time in both trials (P=0.000 and P=0.042, respectively).<br><br>Secondary:<br>Not reported |
| Vuurman et al.[60] (1996) | DB, PG, RCT<br><br>Atopic subjects 16 | N=104<br><br>14 days | Primary:<br>Symptom scores, memory test, | Primary:<br>There were significant improvements in symptoms on day 1 with diphenhydramine and acrivastine plus pseudoephedrine compared to |

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| Diphenhydramine 50 mg QD<br><br>vs<br><br>acrivastine 8 mg and pseudoephedrine 60 mg QD administered as a fixed-dose combination<br><br>vs<br><br>placebo | to 25 years of age with seasonal allergic rhinitis requiring antihistamine therapy and matched controls who did not require antihistamine therapy | | learning test, examination performance<br><br>Secondary:<br>Not reported | placebo (P=0.024 and P=0.029, respectively). There were no significant treatment effects on day two or day three. At examination, symptom scores were not significantly different between groups.<br><br>There was no overall treatment effects regarding the number of words during immediate recall (P=0.761); however, there was a significant increase over time in overall performance (P<0.001). Analysis of the scores for each day showed no significant differences between the groups on any day. There was no overall effect of treatment found on any day, or over all days, in mean delayed recall results; however, there was a significant increase over time (P<0.001).<br><br>Training and examination scores increased in all groups. Atopic subjects had significantly lower scores than the control group (P=0.043). There was a significant performance deficiency noted after administration of diphenhydramine in atopic subjects compared to controls (P<0.001). Performance after acrivastine plus pseudoephedrine was significantly better than after administration of diphenhydramine (P=0.001). The difference between placebo and diphenhydramine was not significant (P=0.067). Performance after acrivastine plus pseudoephedrine was not significantly different from placebo (P=0.13) or controls (P=0.87).<br><br>Atopic subjects performed significantly worse than controls in the performance at examination analysis (P=0.012). There was a significant performance deficiency noted after administration of diphenhydramine in atopic subjects compared to controls (P<0.001). The mean performance after acrivastine plus pseudoephedrine was significantly better than after administration of diphenhydramine (P=0.001). Performance after acrivastine plus pseudoephedrine was not significantly different from the control group (P=0.73).<br><br>Secondary:<br>Not reported |
| Simons et al.[61] (1996)<br><br>Diphenhydramine | DB, PC, RCT, XO<br><br>Healthy men 18 to 40 years of age | N=15<br><br>>7 weeks | Primary:<br>Cognitive function assessed using the P300-event-related | Primary:<br>The percent change in the P300 latency from baseline from least to greatest was: terfenadine, placebo, cetirizine, ketotifen, loratadine, astemizole and diphenhydramine. Diphenhydramine increased the P300 |

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| 50 mg as a single dose<br><br>vs<br><br>astemizole 10 mg as a single dose<br><br>vs<br><br>cetirizine 10 mg as a single dose<br><br>vs<br><br>ketotifen 2 mg as a single dose<br><br>vs<br><br>loratadine 10 mg as a single dose<br><br>vs<br><br>terfenadine† 60mg as a single dose<br><br>vs<br><br>placebo | | | potential, and subjective assessment of somnolence using a VAS<br><br>Secondary:<br>Not reported | latency significantly compared with baseline and with placebo.<br><br>The mean change in the visual analogue scale for somnolence from least to greatest was: placebo, astemizole, terfenadine, loratadine, cetirizine, ketotifen and diphenhydramine. Somnolence was significantly greater than baseline after astemizole, terfenadine and loratadine. It was also significantly greater than baseline and placebo after cetirizine, ketotifen and diphenhydramine.<br><br>The effect of terfenadine, cetirizine, ketotifen, loratadine, and astemizole on the P300 latency and the visual analogue scale did not differ significantly from that of diphenhydramine.<br><br>Secondary:<br>Not reported |
| Schweitzer et al.[62] (1994)<br><br>Diphenhydramine 50 mg TID for 3 consecutive days | DB, RCT, XO<br><br>Healthy atopic adults | N=12<br><br>>28 days | Primary:<br>MSLT, SALT, VAS sleepiness ratings, global sleepiness and performance | Primary:<br>*MSLT*<br>Mean sleep latencies were 7.5, 5.5, and 7.8 minutes on day one for cetirizine, diphenhydramine, and placebo, respectively, and 8.0, 8.3, and 8.3 minutes on day three. |

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| vs<br><br>cetirizine 10 mg for 3 consecutive days QD<br><br>vs<br><br>placebo | | | ratings<br><br>Secondary:<br>Not reported | On day one, diphenhydramine produced significant sedation at 1:00 PM and 5:00 PM relative to placebo (P<0.05) and at 11:00 AM (P=0.056) and 1:00 PM (P<0.05) compared with cetirizine. There were no differences between placebo and cetirizine on treatment day 1 and no differences among the three conditions on treatment day three.<br><br>There was a significant decrease in physiologic sleepiness with diphenhydramine on day three compared with day one (P<0.05). During both treatment days, physiologic sleepiness was maximal at 11:00 AM and generally decreased as the day progressed for all conditions.<br><br>*SALT*<br>On day 1, subjects made fewer correct responses with diphenhydramine (83.1%) than with cetirizine (87.8%) or placebo (88.9%; P<0.05 for both). On day 3, correct response rate was equivalent among the three treatment groups.<br><br>Performance improved on day three (compared with day one) in the diphenhydramine group (P<0.05), whereas performance remained stable on day three in the other two treatment groups. Performance was most impaired on day one during the two morning test periods after diphenhydramine administration and was impaired to a lesser extent in the afternoon after the second diphenhydramine dose.<br><br>On treatment day one, subjects responded twice as quickly to assembly line malfunctions in the cetirizine and placebo groups (1.3 seconds and 1.2 seconds, respectively) compared with diphenhydramine (2.6 seconds, P<0.05 for both). Response time with diphenhydramine improved on day 3 (1.7 seconds, P<0.05 compared with day one).<br><br>*VAS Sleepiness Ratings*<br>Subjects rated themselves as 20% sleepier with diphenhydramine compared with placebo (P<0.05) and 14% sleepier compared with cetirizine (P=0.08). Subjective ratings of sleepiness did not differ between cetirizine and placebo.<br><br>Subjects rated themselves as slightly more alert on day three compared |

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| | | | | with day one. Subjects judged that they were sleepiest at 11:00 AM and 3:00 PM. On day one, diphenhydramine produced significantly more subjective sleepiness than placebo at 11:00 AM, 1:00 PM, 3:00 PM, and 5:00 PM (P<0.05).<br><br>*Global Sleepiness and Performance Ratings*<br>Subjects rated themselves as being more sleepy at the end of diphenhydramine treatment on day one compared with cetirizine and placebo (P<0.05 for both), which did not differ from each other. On treatment day three, there were no significant differences among the three groups.<br><br>Subjects rated themselves as being significantly more alert at the end of day three in the diphenhydramine condition compared with treatment day one (P<0.001), whereas alertness ratings were similar on both treatment days for cetirizine and placebo.<br><br>Performance was poorer on day one with diphenhydramine compared with cetirizine (P<0.01) and placebo (P=0.083), which did not differ from each other. Performance ratings improved on day 3 with diphenhydramine compared to day one (P<0.01). Performance ratings during the cetirizine and placebo conditions were similar on both treatment days. There were no significant differences among the three groups on day three.<br><br>Secondary:<br>Not reported |
| Simons et al.[63] (1999)<br><br>Diphenhydramine 50 mg as a single dose<br><br>vs<br><br>chlorpheniramine 8 mg as a single | DB, PC, RCT, XO<br><br>Healthy subjects >65 years of age | N=15<br><br>>5 weeks | Primary:<br>Cognitive function assessed using the P300-event-related potential, and subjective assessment of somnolence using a VAS<br><br>Secondary: | Primary:<br>The change in the P300 latency from baseline from least to greatest was: cetirizine, placebo, loratadine, diphenhydramine, and chlorpheniramine. However, there were no significant differences in the in P300 latency measurements at 2 to 2.5 hours after dosing compared to predose values (P>0.05).<br><br>The change in VAS for somnolence from least to greatest was: placebo, loratadine, cetirizine, chlorpheniramine, and diphenhydramine. There were no significant differences in the subjective assessment of somnolence 2 to 2.5 hours after dosing compared to predose values (P>0.05). |

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| dose<br><br>vs<br><br>cetirizine 10 mg as a single dose<br><br>vs<br><br>loratadine 10 mg as a single dose<br><br>vs<br><br>placebo | | | Not reported | Secondary:<br>Not reported |
| Vuurman et al.[64] (2004)<br><br>Diphenhydramine 50 mg as a single dose<br><br>vs<br><br>desloratadine 5 mg as a single dose<br><br>vs<br><br>placebo | AC, DB, PC, RCT, XO<br><br>Healthy volunteers | N=18<br><br>>3 weeks | Primary:<br>Driving performance (SDLP) and psychomotor performance<br><br>Secondary:<br>Not reported | Primary:<br>In the highway driving test, significantly more weaving behavior occurred following treatment with diphenhydramine (P<0.001 vs desloratadine or placebo). The mean SDLP was comparable following treatment with desloratadine or placebo. Subjects maintained a more constant speed with desloratadine than with diphenhydramine treatment (P=0.045); there was no significant difference between desloratadine and placebo.<br><br>In the car-following test, mean brake reaction time was significantly shorter with desloratadine than with placebo (P=0.033) or diphenhydramine (P=0.001). No significant difference was observed between the diphenhydramine and placebo groups. No significant differences were observed among the groups with regard to headway variability.<br><br>Subjects treated with diphenhydramine demonstrated a significantly greater increase in sleepiness score from baseline compared with desloratadine (P<0.001) or placebo (P<0.001). No difference was observed between the desloratadine and placebo groups.<br><br>Mean tracking error significantly increased from baseline following treatment with diphenhydramine compared with desloratadine and placebo |

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| | | | | (P=0.002 and P=0.001, respectively). Diphenhydramine significantly increased mean reaction time compared with desloratadine (P=0.014). There was no significant difference between desloratadine and placebo for either of these parameters.<br><br>Secondary:<br>Not reported |
| Wilken et al.[65] (2003)<br><br>Diphenhydramine 50 mg as a single dose<br><br>vs<br><br>desloratadine 5 mg as a single dose<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Healthy adults 18 to 60 years of age with ragweed induced allergic rhinitis | N=248<br><br>1 week | Primary:<br>Vigilance and cognitive performance battery; symptom evaluation<br><br>Secondary:<br>Not reported | Primary:<br>Subjects taking diphenhydramine performed significantly worse on all parameters of vigilance compared with subjects taking either desloratadine or placebo.<br><br>Subjects taking diphenhydramine performed significantly worse on measures across other cognitive domains (working memory, psychomotor speed, reasoning/computation, divided attention) compared with subjects taking either desloratadine or placebo. There were no statistically significant differences between subjects taking placebo and those taking desloratadine on any of the measures of cognitive functioning.<br><br>Subjects taking diphenhydramine reported significantly worse functioning on the performance battery (P<0.001) compared with subjects taking desloratadine or placebo. Subjects in the diphenhydramine group reported a significantly greater degree of sedation (P<0.001) following the completion of the Stanford Sleepiness Scale test battery than subjects taking either desloratadine or placebo. Subjects taking diphenhydramine reported being significantly drowsier, more lethargic, and less clear-headed, quick-witted, attentive, coordinated, and proficient than subjects taking desloratadine or placebo. Subjects in the desloratadine group reported being significantly more clear-headed (P=0.05) and less drowsy (P=0.046) than those in the placebo group.<br><br>Desloratadine and diphenhydramine treatment led to significant reductions in TTSs (P<0.001 and P<0.04, respectively) and TNSSs (P<0.001 and P<0.046, respectively) compared to placebo. There was a significant improvement in nonnasal symptoms for subjects taking diphenhydramine (P<0.001) compared with subjects taking placebo; however, this finding was not significant for desloratadine. Self-reported global therapeutic |

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| | | | | response was significantly better in subjects taking either desloratadine (P=0.03) or diphenhydramine (P<0.001) compared with placebo.<br><br>Secondary:<br>Not reported |
| Mansfield et al.[66] (2003)<br><br>Diphenhydramine 50 mg as a single dose<br><br>vs<br><br>fexofenadine 180 mg as a single dose<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Healthy volunteers | N=44<br><br><40 days | Primary:<br>Cognitive performance using the Test of Variables of Attention<br><br>Secondary:<br>Not reported | Primary:<br>Mean response time was significantly longer with diphenhydramine than with placebo (P=0.0230). There was no significant difference between fexofenadine and placebo (P=0.5264), nor was there a significant difference between fexofenadine and diphenhydramine (P=0.1258).<br><br>There was a significant difference in the average omission error values between diphenhydramine and placebo (P=0.0398). Fexofenadine and placebo were not statistically different (P=0.6389) nor was fexofenadine and diphenhydramine (P=0.1028).<br><br>The frequency of commission errors was not significantly different for diphenhydramine or fexofenadine compared to placebo (P=0.4975 and P=0.1483, respectively). However, diphenhydramine was associated with significantly more commission errors than fexofenadine (P=0.0354).<br><br>Diphenhydramine was associated with significantly more drowsiness than placebo (P=0.0004). Fexofenadine was not statistically different from placebo for drowsiness scores (P=0.0810).There was no significant difference in drowsiness with diphenhydramine compared to fexofenadine (P=0.0742).<br><br>Secondary:<br>Not reported |
| Weiler et al.[67] (2000)<br><br>Diphenhydramine 50 mg as a single dose<br><br>vs | DB, RCT, XO<br><br>Licensed drivers with seasonal allergic rhinitis | N=41<br><br>4 weeks | Primary:<br>Driving performance (using the Iowa Driving Simulator) and self-reported drowsiness | Primary:<br>*Phase 1*<br>After taking diphenhydramine, participants performed car-following with significantly less coherence than after taking alcohol, fexofenadine, or placebo (95% CI excludes zero).<br><br>Significant differences in minimum following distance were observed among the four treatments. When participants performed car-following |

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| fexofenadine 60 mg as a single dose<br><br>vs<br><br>alcohol (~0.1% blood alcohol concentration)<br><br>vs<br><br>placebo | | | Secondary:<br>Not reported | after consuming alcohol, they had significantly smaller minimum following distances than they did after taking fexofenadine or placebo. There was no significant difference in car-following after taking diphenhydramine and alcohol.<br><br>After participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol, but not placebo. After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine.<br><br>*Phase 2*<br>After completing phase 1, participants drove the remaining 30 miles of the course "as you normally would drive."<br><br>After participants took fexofenadine, they had significantly less steering instability than after taking diphenhydramine or alcohol, but not placebo. After participants took placebo, they had significantly less steering instability than after consuming alcohol or diphenhydramine. After participants consumed alcohol, they had the same or less steering instability than after taking diphenhydramine.<br><br>No significant differences for lane excursions to the right were noted among the four treatments. Significant differences were noted the four treatments for excursions to the left. After participants took diphenhydramine, they crossed the center line significantly more often than after taking fexofenadine or placebo. After participants took alcohol, they crossed the center line significantly more often than after taking fexofenadine and placebos. Fexofenadine and placebo did not differ significantly.<br><br>There were no significant differences among the treatment groups on response time to a blocking vehicle. However, after consuming alcohol, participants responded more slowly to the event than after they took fexofenadine. Responses to the blocking vehicle were categorized as clear avoidance, potentially unsafe avoidance, or collision. The overall differences were not significant. |

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| | | | | Drowsiness scores on the second visual analogue scale (given 1 hour after treatment administration) were not significantly different among the treatment groups. At the time of the third visual analogue scale (just before the drive), participants were significantly more drowsy after taking diphenhydramine and least drowsy after taking fexofenadine or placebo. The differences between diphenhydramine and fexofenadine or placebo were significant. After the drive, participants were most drowsy with diphenhydramine and least drowsy with placebo. The difference between fexofenadine and placebo was not significant. Participants reported significantly higher levels of drowsiness with diphenhydramine than with fexofenadine and placebo.<br><br>Secondary:<br>Not reported |
| Gandon et al.[68] (2002)<br><br>Diphenhydramine 50 mg QD for 5 consecutive days<br><br>vs<br><br>levocetirizine 5 mg QD for 5 consecutive days<br><br>vs<br><br>placebo | XO<br><br>Healthy volunteers | N=19<br><br>>1 month | Primary:<br>CFF<br><br>Secondary:<br>CRT, body sway, LMT, and subjective assessments of alertness | Primary:<br>The mean CFF values for levocetirizine and placebo were not significantly different from each other globally across all time points (P=0.292) or at any specific time point. Mean CFF values after diphenhydramine administration was significantly different than placebo across all time points (P=0.019) and at one, two and three hours after dosing (P<0.04).<br><br>Secondary:<br>Mean CRT scores were comparable over time for the three treatments, with no significant differences for groups on day five.<br><br>With regards to body sway, results on distance and surface displacement from the center of gravity (measured with eyes open or closed) were similar for levocetirizine and placebo. An increase in total displacement distance was demonstrated up to three hours after dosing with diphenhydramine on day one (eyes closed: 16.35 cm (95% CI, 5.61 to 27.10).<br><br>Scores of alertness increased after levocetirizine and placebo. A decrease in alertness was observed after diphenhydramine administration on day one compared with placebo.<br><br>There was a similar evolution of contentedness in all three treatments on |

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| | | | | days one and five. There was no consistent decrease in calmness observed with any treatment. There was no significant difference in LMT among the three treatment groups. |
| Verster et al.[69] (2003)<br><br>Diphenhydramine 50 mg as a single dose on 4 consecutive days<br><br>vs<br><br>levocetirizine 5 mg as a single dose on 4 consecutive days<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Healthy volunteers | N=48<br><br>>3 weeks | Primary:<br>Memory, psychomotor performance, mood<br><br>Secondary:<br>Not reported | Primary:<br>On the word learning test, learning was not significantly impaired after administration of either levocetirizine or diphenhydramine compared to placebo on day one or day four.<br><br>On the Sternberg Memory Scanning Test, there were no significant differences in reaction time or percentage of errors made during test performance between the treatments and placebo on day one. On day four, there were no significant differences on memory-scanning parameters between the treatments and placebo.<br><br>On the tracking test, tracking ability after administration of diphenhydramine was significantly impaired in both the easy and hard versions of the test on day one (P<0.0001 for both). Tracking ability after administration of levocetirizine was not significantly impaired compared to placebo. On day four, there were no significant differences between the treatments and placebo.<br><br>On the divided attention test, tracking ability after administration of diphenhydramine was significantly different from that after placebo on day one (P<0.0001). Tracking ability after administration of levocetirizine was not significantly different from that after placebo. Compared to placebo, reaction times after administration of diphenhydramine were significantly increased (P<0.0001). Reaction times with levocetirizine did not change. On day four, there were no significant differences between treatments and placebo on divided attention test parameters.<br><br>After administration of diphenhydramine, scores on the ARCI-49 questionnaire indicated significantly increased sedation on days one and four. Euphoria, intellectual efficacy and energy were significantly decreased with diphenhydramine. The effects of levocetirizine on all ARCI-49 scales were not significantly different from the effects of placebo. |

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| | | | | Secondary:<br>Not reported |
| Verster et al.[70] (2003)<br><br>Diphenhydramine 50 mg as a single dose on 4 consecutive days<br><br>vs<br><br>levocetirizine 5 mg as a single dose on 4 consecutive days<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Healthy volunteers | N=48<br><br>>3 weeks | Primary:<br>Driving performance (SDLP) and subjective assessments<br><br>Secondary:<br>Not reported | Primary:<br>When assessing the acute effects of treatment, the majority of individual SDLPs after levocetirizine were similar to placebo (P=not significant). Only 16.7% of subjects drove worse than the acceptance limit. For those receiving diphenhydramine, 43.8% drove worse than the legal limit (for driving in The Netherlands; P<0.0001). The SDLP of diphenhydramine differed significantly from placebo (P<0.0001). No significant effects were found for the other parameters of the driving test.<br><br>When assessing the sub-chronic effects of treatment, the majority of individual SDLPs after levocetirizine were similar to placebo (P=not significant). Only 16.7% of subjects drove worse than the acceptance limit. For those receiving diphenhydramine, 31.1% of subjects drove worse than the legal limit (for driving in The Netherlands; P<0.001). The SDLP of diphenhydramine differed significantly from placebo (P<0.0003). No significant effects were found for the other parameters of the driving test.<br><br>In the subjective assessment (acute treatment), diphenhydramine significantly reduced driving quality (P<0.0001), increased mental effort during driving (P<0.0001), and reduced alertness (P<0.0001). There were no significant differences found between levocetirizine and placebo.<br><br>In the subjective assessment (sub-chronic treatment), driving quality and mental effort during driving did not differ significantly between the treatments. Alertness was significantly reduced after diphenhydramine compared to placebo (P<0.005). The level of alertness did not differ between levocetirizine and placebo.<br><br>Secondary:<br>Not reported |
| Bender et al.[71] (2001)<br><br>Diphenhydramine | DB, PC, PG, RCT<br><br>Children 8 to 10 years of age with | N=63<br><br>15 days (4 laboratory | Primary:<br>Total Verbal Instruction Score, Total Reading | Primary:<br>In the Verbal Instruction Score, no significant treatment-group differences were found. Errors decreased significantly with age (P<0.0001) and over time (P<0.0001) as familiarity with materials and testing situations |

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| 25 mg twice daily (6 hours apart) on 3 different school days<br><br>vs<br><br>loratadine 10 mg QD on 3 different days<br><br>vs<br><br>placebo | allergic rhinitis requiring an antihistamine | school days) | Recall Score, Total Average Reaction Time, and Somnolence Scale using a computer-administered neuropsychologic test battery (administered on four school days)<br><br>Secondary:<br>Not reported | increased.<br><br>In the Reading Test Score, no significant treatment-group differences were found. Both age and baseline reading ability were significant covariates (P<0.0001), and errors decreased markedly over time (P<0.0001).<br><br>For Average Reaction Time, no treatment-group differences were found for reaction time or performance scores on any of the four visits. Average reaction time to computer tasks decreased over all four visits (P<0.0001).<br><br>For Somnolence Scale ratings, there was no significant differences between treatment groups (P=0.17).<br><br>Secondary:<br>Not reported |
| Kay et al.[72] (1997)<br><br>Diphenhydramine 50 mg for 1 dose on day 1, then 25 mg QID<br><br>vs<br><br>loratadine 10 mg QD<br><br>vs<br><br>placebo | DB, RCT<br><br>Healthy volunteers | N=98<br><br>5 days | Primary:<br>Cognitive and psychomotor test performance on day one, day three, and day five, as well as self-reported measures<br><br>Secondary:<br>Not reported | Primary:<br>*Day 1*<br>Subjects receiving diphenhydramine performed poorly compared with subjects receiving loratadine or placebo on measures of divided attention, working memory, and vigilance. Compared to placebo, loratadine did not adversely affect performance on any of these measures.<br><br>Subjects receiving diphenhydramine demonstrated poorer performance on a measure of tracking accuracy under divided attention conditions (Cog Screen Dual Task Test) compared with subjects taking loratadine or placebo. Subjects taking loratadine outperformed subjects taking placebo (P=0.02).<br><br>Subjects taking diphenhydramine were less efficient in their performance on the Complex Cognitive Assessment Battery Mark Numbers Test than subjects taking loratadine (P=0.002).<br><br>Subjects taking diphenhydramine obtained lower accuracy scores on the ANAM Running Memory Test compared with subjects taking loratadine (P=0.008). ANAM Math throughput scores were also lower for subjects taking diphenhydramine (P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | The CogScreen Shifting Attention Test-Instruction Condition throughput score was higher for subjects who received loratadine (P<0.05) than for subjects taking diphenhydramine.<br><br>On the Kay Continuous Performance Test, subjects taking diphenhydramine were more likely to make errors of commission and errors of omission (P=0.05 and P=0.002, respectively).<br><br>Ratings of sleepiness on the Stanford Sleepiness Scale were higher after diphenhydramine than after administration of loratadine (P=0.02). Subjects receiving diphenhydramine reported higher levels of fatigue than subjects receiving loratadine (P<0.001). Subjects receiving diphenhydramine also had lower levels of motivation (P<0.001) and rated the quality of their test performance as lower (P<0.001), compared with subjects receiving loratadine.<br><br>*Days three and five*<br>There were no differences among the treatment groups for the cognitive and psychomotor tests performed on days three and five. However, subjects who received diphenhydramine performed less well than subjects who received placebo on days three and five on a test of tracking errors. There were no differences between loratadine and placebo on the cognitive and psychomotor tests on day five.<br><br>Subjects who received diphenhydramine reported greater fatigue (P=0.001) and rated the quality of their test performance as lower (P=0.007) compared with subjects who received loratadine. Subjects in the diphenhydramine group also reported lower motivation than subjects taking loratadine (P=0.001). Loratadine did not differ significantly from placebo with respect to level of motivation, mood, or self appraised quality of performance on day five.<br><br>Secondary:<br>Not reported |
| Vuurman et al.[73] (1993) | RCT<br><br>Children 10 to 12 | N=52<br><br>14 days | Primary:<br>Factual knowledge scores, conceptual | Primary:<br>For factual knowledge scores, atopic children were significantly less knowledgeable than children in the control group (P<0.01). Paired |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Diphenhydramine 25 mg BID (4 hours apart) for 2 weeks<br><br>vs<br><br>loratadine 10 mg QD for 2 weeks<br><br>vs<br><br>placebo | years of age with seasonal allergic rhinitis requiring antihistamine therapy and matched controls who did not require antihistamine therapy | | knowledge scores, composite learning scores<br><br>Secondary:<br>Not reported | comparisons of the atopic group with controls showed a significant effect of diphenhydramine (P=0.012).<br><br>For conceptual knowledge scores, atopic children were significantly less knowledgeable than children in the control group (P=0.001). Paired comparisons of the atopic group with controls showed a significant effect of diphenhydramine (P=0.001).<br><br>Geometric mean survival years (knowledge application scores) were significantly lower in children receiving antihistamines compared to the control group (P<0.02).<br><br>The composite learning scores were significantly lower in atopic children compared to the control group (P<0.003). Composite learning scores were also lower in atopic children receiving placebo or diphenhydramine compared to the control group (P=0.007 and P=0.002, respectively).<br><br>Secondary:<br>Not reported |
| Roth et al.[74] (1987)<br><br>Diphenhydramine 50 mg TID for 2 days<br><br>vs<br><br>loratadine 10 mg QD for 2 days<br><br>vs<br><br>loratadine 40 mg QD for 2 days<br><br>vs | DB, RCT, XO<br><br>Healthy adults 19 to 35 years of age | N=16<br><br>28 days | Primary:<br>Measures of performance and daytime sleepiness<br><br>Secondary:<br>Not reported | Primary:<br>The nocturnal polysomnogram did not detect any difference among the treatments on any parameter evaluated, including total sleep time, latency to sleep, number and duration of awakenings after sleep onset, and percentages of various sleep stages.<br><br>There was a significant reduction (increased sleepiness) in mean latency to sleep (P<0.01) with diphenhydramine compared to placebo (P<.01) and both loratadine doses (P<0.01 and P<0.02). The low loratadine dose did not differ from the placebo dose or from the large loratadine dose. Although the high loratadine dose did not differ from the low loratadine dose, it did differ from the placebo dose (P<0.04).<br><br>Subjects rated themselves as being sleepier with diphenhydramine.<br><br>The vigilance and reaction time tasks demonstrated no effect of treatments. On the performance battery at 9:30 A.M., diphenhydramine produced decrements in digit symbol substitution (P<0.05), whereas both |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| placebo | | | | loratadine doses had no effects. The afternoon performance battery (1:30 P.M.) demonstrated no effects of the treatments.<br><br>Secondary:<br>Not reported |
| Witek et al.[75] (1995)<br><br>Study1<br>Diphenhydramine 50 mg as a single dose<br><br>vs<br><br>terfenadine† 60 mg as a single dose<br><br>vs<br><br>placebo<br><br>Study 2<br>Diphenhydramine 25 mg as a single dose<br><br>vs<br><br>diphenhydramine 50 mg as a single dose<br><br>vs<br><br>chlorpheniramine 4 mg as a single | DB, PC, RCT, XO<br><br>Healthy volunteers 18 to 45 years of age | Study1<br>N=18<br><br>>1 week<br><br>Study 2<br>N=20<br><br>>1 week | Primary:<br>Subjective assessments and psychomotor performance<br><br>Secondary:<br>Not reported | Primary:<br>*Study 1*<br>In the subjective assessments, diphenhydramine-induced sleepiness was significantly greater than that reported after terfenadine or placebo (P<0.05). There was no difference in sleepiness between terfenadine and placebo. In the VAS analysis, subjects receiving diphenhydramine reported significantly higher levels of sleepiness at three and five hours after taking the dose than after taking terfenadine or placebo (P<0.05). No significant differences were noted between terfenadine and placebo. Significant reductions in alertness were reported with diphenhydramine compared to terfenadine or placebo at three hours after dosing (P<0.05). The difference between diphenhydramine and terfenadine was still evident five hours after dosing (P<0.05).<br><br>CRT significantly increased one and three hours after diphenhydramine compared with terfenadine. Diphenhydramine produced significant increases in reaction time relative to placebo three hours after drug. No significant differences between terfenadine and placebo were found. There were significant impairments with diphenhydramine in tracking ability compared to terfenadine or placebo at one and three hours.<br><br>*Study 2*<br>In the subjective assessments, all antihistamine treatments resulted in significantly higher scores on the Stanford Sleepiness Scale three hours after dosing than those reported after placebo (P<0.05). Sleepiness scores were significantly higher with diphenhydramine 50 mg than diphenhydramine 25 mg three hours after dosing and significantly higher than chlorpheniramine five hours after dosing. In the VAS analysis, all three antihistamines produced significantly higher sleepiness compared to placebo three hours after drug administration (P<0.05). Significant reductions in alertness were reported with diphenhydramine 50 mg. There were no significant differences among treatments in jitteriness self- |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| dose<br><br>vs<br><br>placebo | | | | assessments.<br><br>All three antihistamines impaired reaction relative to placebo one and three hours after dosing (P<0.05). Chlorpheniramine resulted in prolonged reaction time seven hours after dosing, which was significantly greater than the response following diphenhydramine 25 mg.<br><br>Tracking was significantly impaired with diphenhydramine (25 and 50 mg) compared to placebo one hour after dosing. At three hours after dosing, diphenhydramine 25 mg significantly impaired tracking relative to placebo and chlorpheniramine.<br><br>Secondary:<br>Not reported |
| Cohen et al.[76] (1985)<br><br>Triprolidine 2.5 mg as a single dose<br><br>vs<br><br>triprolidine 5 mg as a single dose<br><br>vs<br><br>acrivastine 4 mg as a single dose<br><br>vs<br><br>acrivastine 8 mg as a single dose<br><br>vs | DB, PC, XO<br><br>Healthy volunteers | N=12<br><br>1 days | Primary:<br>10-minute tracking test score, reaction time, subjective effects using a VAS<br><br>Secondary:<br>Not reported | Primary:<br>Triprolidine (2.5 and 5 mg) decreased the time tracking score at 1.5 hours after drug dosing compared with placebo and all the acrivastine treatments. The mean tracking score continued to be impaired three hours after triprolidine (5 mg). None of the acrivastine treatments caused any significant impairment compared to placebo.<br><br>Reaction time was increased at 1.5 hours after triprolidine (2.5 and 5 mg) compared with placebo, and at three hours (triprolidine 5 mg). None of the treatments were different from placebo 5 hours after drug dosing. None of the acrivastine treatments caused a significant change in reaction time compared with placebo at any time during the study.<br><br>Triprolidine (2.5 and 5 mg) made subjects feel drowsy, clumsy, lethargic, mentally slow, dreamy, and bored at 1.5 hours after drug dosing compared to placebo. Triprolidine (5 mg) also made them feel muzzier and more incompetent. No effects were noted after any of the acrivastine doses. Effects were seen 3 hours after triprolidine (5 mg) as the subjects felt clumsy, lethargic, and mentally slow.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| acrivastine 16 mg as a single dose<br><br>vs<br><br>placebo | | | | |

†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, SR=sustained-release, TID=three times daily
Study design abbreviations: AC=active control, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, XO=cross-over
Miscellaneous abbreviations: ANAM=Automated Neuropsychological Assessment Metrics, ARCI=Addiction Research Center Inventory, CFF=critical flicker fusion, CI=confidence interval, CRT=choice reaction time, CTT=compensatory tracking test, LARS=line analogue rating scale, LMT=learning memory test, MSLT=multiple sleep latency test, NAR=nasal airway resistance, PSV=peak saccade velocity, RVIP=rapid visual information processing, SALT=simulated assembly line task, SDLP=standard deviation of lateral position, TAR=total airflow rates, TNSS=total nasal symptom scores, TSS=total symptom scores, VAS=visual rating scale, WA=wrist actigraphy

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 9. Relative Cost of the First Generation Antihistamines**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| **Ethanolamine Derivatives** | | | | |
| Carbinoxamine | liquid, tablet | Arbinoxa®* | $-$$$$ | $ |
| Clemastine | syrup, tablet | Tavist-1®*‡ | $-$$$ | $ |
| Diphenhydramine | capsule, chewable tablet, elixir, injection, liquid, syrup, tablet | N/A | N/A | $ |
| Doxylamine | chewable tablet, tablet | Aldex-AN®‡ | $$$$$ | N/A |
| Phenylephrine and diphenhydramine | chewable tablet | Aldex CT®‡ | $$$$$ | N/A |
| **Ethylenediamine Derivatives** | | | | |
| Phenylephrine and pyrilamine | suspension, tablet | Aldex D®‡, Poly Hist Forte®‡ | $$$-$$$$ | N/A |
| **Propylamine Derivatives** | | | | |
| Brompheniramine | drops, | J-Tan PD®‡ | $$$$$ | N/A |
| Chlorpheniramine | extended-release tablet, syrup, tablet | N/A | N/A | $ |
| Dexchlorpheniramine | syrup | N/A | N/A | N/A |
| Phenylephrine and | suspension | Vazobid-PD®‡ | $$ | N/A |

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| brompheniramine | | | | |
| Phenylephrine and chlorpheniramine | drops, liquid, tablet | Cardec®*‡, Dallergy®*‡, Ed Chlorped D®‡, Lohist®‡ | $ | $-$$$ |
| Phenylephrine, pyrilamine, and chlorpheniramine | suspension | Phena-S 12® | N/A | N/A |
| Pseudoephedrine and brompheniramine | drops, liquid | J-Tan D PD®‡ | $$$$$ | N/A |
| Pseudoephedrine and chlorpheniramine | drops, liquid, tablet | Neutrahist®*‡ | $$$$$ | $ |
| Pseudoephedrine and triprolidine | liquid, syrup, tablet | Ed A-Hist Pse®*‡, Pediatex TD®*‡ | $$$ | $$$ |

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
N/A=Not available

## X. Conclusions

The first generation antihistamines are approved for the treatment of allergic and non-allergic conditions; however, they are primarily used for the management of allergic rhinitis, urticaria and angioedema. They are available as single entity agents, as well as in combination with other first generation antihistamines and oral decongestants. The majority of the products are available in a generic formulation or over-the-counter.

There are several organizations that provide recommendations on the use of first generation antihistamines. There are a variety of effective treatment options for allergic rhinitis, including $H_1$-antihistamines. The second generation antihistamines are preferred over first generation agents because they have a lower tendency to cause sedation, anticholinergic effects and performance impairment.[1,10] Due to their pharmacokinetic properties (prolonged half-life and active metabolites), the central nervous system effects cannot be eliminated by administering these agents at bedtime.[1] For the treatment of urticaria, antihistamines are the cornerstone of therapy. Second generation antihistamines are generally preferred; however, first generation agents can also be effective and well-tolerated by patients. The addition of a sedating first generation antihistamine to a second generation antihistamine may help patients sleep better.[2,3] For the treatment of atopic dermatitis, topical corticosteroids are the standard of care.[6] Antihistamines may help relieve pruritic symptoms, especially in those with concomitant urticaria or allergic rhinitis.[7] First generation antihistamines may also be useful in patients with sleep disturbances due to pruritus.[6,7] For the management of allergic/atopic conjunctivitis, topical antihistamines are an effective treatment option; however, oral antihistamines may also be considered.[8] Antihistamines are not recommended for the treatment of acute sinusitis. They may have a role in the management of chronic sinusitis if allergic rhinitis is an underlying risk factor.[9,12,13] The available guidelines do not give preference to one particular first generation antihistamine over another.[1-3,5-13]

There are very few studies that directly compare the first generation antihistamines. Clemastine and chlorpheniramine were found to be equally effective for the treatment of allergic rhinitis.[38-40] The first generation antihistamines have also been shown to be as effective as second generation antihistamines in multiple studies.[34,36-44,46,51] The fixed-dose combination of triprolidine/pseudoephedrine was shown to be more effective than monotherapy with triprolidine or pseudoephedrine.[47-49] However, there were no studies found in the medical literature that directly compared the efficacy of the fixed-dose combination product to the coadministration of each component as separate formulations. Several clinical trials have evaluated the central nervous system effects of antihistamines. The first generation antihistamines have been shown to adversely affect cognitive and psychomotor functions, as well as impair driving performance.[53-76]

Oral decongestants (pseudoephedrine and phenylephrine) help to relieve nasal congestion and are available in combination with several of the first generation antihistamines. Pseudoephedrine has been used to make methamphetamine and there are restrictions on the sale of this product in the United States. Many over-the-

counter products now contain phenylephrine; however, phenylephrine appears to be less effective than pseudoephedrine as it is extensively metabolized in the gut.[1]

There is insufficient evidence to support that one brand first generation antihistamine is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand first generation antihistamine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

## XII. References

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Estrogens
# AHFS Class 681604
# November 14, 2012

## I. Overview

The estrogens are approved for the treatment of vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, abnormal uterine bleeding, hypoestrogenism, prevention of postmenopausal osteoporosis, as well as for the palliative treatment of prostate and breast cancer.[1-34] The menopausal transition period is associated with irregular or heavy bleeding, hot flashes, sleep disturbance, vaginal dryness, sexual dysfunction, incontinence, urinary tract infections, depression, as well as other clinical manifestations. For most women, these symptoms are usually mild and of short duration. The use of hormone therapy helps to alleviate these symptoms. Estrogen can be used alone in women who have had a hysterectomy; however, a progestin should be added to the regimen for women with an intact uterus as it reduces the risk of endometrial cancer.[35-53]

For over 20 years, studies have examined the role of hormone therapy in the prevention of chronic diseases.[38] Observational studies suggested that there was a lower risk of cardiovascular disease, colorectal cancer and osteoporotic fractures with the use of hormone therapy.[39] The Women's Health Initiative (WHI) studies were designed to further assess the effects of hormone therapy on these end points. Women with an intact uterus were enrolled in the estrogen-plus-progestin therapy (EPT) trial, whereas women without a uterus were enrolled in the estrogen-alone therapy (ET) study. The EPT substudy was stopped early due to an increased risk for cardiovascular events, stroke, pulmonary emboli, venous thromboembolic events and invasive breast cancer.[41] The ET substudy was also stopped early due to an increased risk of stroke and no benefit with regards to cardiovascular disease.[42] Two additional long-term trials (HERS and HERS II) also failed to show a benefit with hormone therapy for the primary or secondary prevention of cardiovascular disease.[43] The Food and Drug Administration requested that the manufacturers of estrogen products revise their product labeling to include updated safety information from the WHI studies.[44,45] Many organizations recommend the use of hormone therapy only for the short-term treatment of menopausal symptoms. The long-term use of hormone therapy is no longer recommended for the prevention of chronic diseases.[38,46,51,52]

The estrogens are available in a variety of dosage forms, including injectable, oral, topical, transdermal and vaginal preparations. Oral estrogens have a greater effect on the liver than topical formulations due to first-pass metabolism following gastrointestinal absorption. Oral estrogens may increase the production of cholesterol (triglycerides and high density lipoprotein cholesterol) and clotting factors, which is only minimally affected by topical, transdermal and vaginal preparations.[40]

The estrogens that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Estradiol, estradiol valerate, estradiol/norethindrone and estropipate are available in a generic formulation. This class was last reviewed in May 2010.

**Table 1. Estrogens Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Estradiol | tablet, topical emulsion, topical gel, topical spray, transdermal patch, vaginal cream, vaginal ring, vaginal tablet | Alora®, Climara®*, Divigel®, Elestrin®, Estrace®*, Estrasorb®, Estring®, Evamist®, Menostar®, Vagifem®, Vivelle-Dot® | estradiol |
| Estradiol acetate | tablet, vaginal ring | Femring®, Femtrace® | none |
| Estradiol cypionate | injection | Depo-Estradiol® | none |
| Estradiol valerate | injection | Delestrogen®* | estradiol valerate |
| Estradiol and drospirenone | tablet | Angeliq® | none |
| Estradiol and levonorgestrel | transdermal patch | Climara Pro® | none |

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Estradiol and norethindrone | tablet, transdermal patch | Activella®*, Combipatch® | estradiol and norethindrone |
| Estradiol and norgestimate | tablet | Prefest® | none |
| Estrogens, conjugated | injection, tablet, vaginal cream | Premarin® | Premarin® (tablets only) |
| Estrogens, conjugated, synthetic A | tablet | Cenestin® | Cenestin® |
| Estrogens, conjugated, synthetic B | tablet | Enjuvia® | none |
| Estrogens, conjugated and medroxyprogesterone | tablet | Premphase®, Prempro® | none |
| Estrogens, esterified | tablet | Menest® | Menest® |
| Estropipate | tablet | N/A | estropipate |
| Norethindrone and ethinyl estradiol | tablet | FemHRT®* | norethindrone and ethinyl estradiol |

*Generic is available in at least one dosage form or strength.
N/A=not applicable.
PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the estrogens are summarized in Table 2. Please note that previous reviews have included clinical guidelines that have either been retired, are no longer available and/or are outdated (i.e., greater than 10 years old).[54,55]

**Table 2. Treatment Guidelines Using the Estrogens**

| Clinical Guideline | Recommendation(s) |
|---|---|
| North American Menopause Society (NAMS): **Management of Osteoporosis in Postmenopausal Women: 2010 Position Statement[48] (2010)** | • The primary indication for estrogen therapy (ET) and combined estrogen-progestogen (EPT) therapy is to treat moderate-to-severe menopausal symptoms.<br>• The primary goal of osteoporosis therapy is fracture prevention. This is accomplished by slowing or stopping bone loss, maintaining bone strength, and minimizing or eliminating factors that may contribute to fractures.<br>• ET/EPT should be used at the lowest effective dose consistent with treatment goals. Lower doses of ET/EPT than used in the Women's Health Initiative (WHI) have not been examined with regard to fracture efficacy.<br>• Extended use of hormone therapy is an option for women who have established reduction in bone mass, regardless of menopause symptoms, for prevention of further bone loss and/or reduction of osteoporotic fracture when other therapies are not appropriate or cause side effects, or when the benefits of extended use are expected to exceed the risks. |
| North American Menopause Society (NAMS): **Estrogen and Progestogen Use in Postmenopausal Women: 2010 Position Statement[46] (2010)** | Benefits and risks of hormone therapy<br>• Use of hormone therapy should be consistent with treatment goals, benefits, and risks for the individual women.<br>• Estrogen therapy, with or without a progesterone, is the most effective treatment for menopause-related vasomotor symptoms and their potential consequences.<br>• Estrogen therapy is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy. When hormone therapy is used for systemic vasomotor symptoms, enquiry about the adequacy of therapy for urogenital atrophy is important. When hormone therapy is considered solely for urogenital atrophy, local vaginal estrogen therapy |

| Clinical Guideline | Recommendation(s) |
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| | is generally recommended.<br>• Relief of moderate to severe vaginal atrophy with systemic or local hormone therapy can be effective in relieving dyspareunia, a common cause of intercourse avoidance. Local estrogen may improve coital satisfaction by improving lubrication and increasing blood flow and sensation in vaginal tissues. Hormone therapy is not recommended as the sole treatment of other problems of sexual function, including decreased libido.<br>• Local estrogen therapy may benefit some women with urge incontinence who have vaginal atrophy. Local estrogen therapy may help reduce the risk of recurrent urinary tract infection.<br>• No statistically significant difference in mean weight gain or body mass index has been demonstrated between women who use hormone therapy and those who do not.<br>• Although no hormone therapy product has regulatory agency approval for enhancing quality of life, an improvement in health-related quality of life can result with hormone therapy use because of decreased menopause symptoms and other mechanisms (e.g., improved sleep, possible elevation of mood that leads to a feeling of well-being).<br>• There is randomized-controlled trial evidence that hormone therapy reduces postmenopausal osteoporotic fractures, including hip fractures, even in women without osteoporosis. No hormone therapy product has regulatory agency approval for treatment of osteoporosis; however, many have approval for prevention of postmenopausal osteoporosis. Extended use of hormone therapy is an option for women who have established reduction in bone mass, regardless of menopause symptoms; for prevention of further bone loss and/or reduction of osteoporotic fracture when alternate therapies are not appropriate due to side effects; or when the benefits of extended use are expected to exceed the risks.<br>• Hormone therapy is currently not recommended as a sole or primary indication for coronary protection in women of any age. Initiation of hormone therapy by women 50 to 59 years of age or by those within 10 years of menopause to treat typical menopause symptoms does not seem to increase the risk of coronary heart disease (CHD) events. There is emerging evidence that initiation of estrogen therapy in early postmenopause may reduce CHD risk.<br>• Although no hormone therapy product has regulatory agency approval to prevent diabetes, large randomized-controlled trials demonstrate that hormone therapy reduces new onset of type 2 diabetes. There is inadequate evidence to recommend hormone therapy as the sole or primary indication for the prevention of diabetes in peri- or postmenopausal women.<br>• Unopposed systemic estrogen therapy in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to the estrogen therapy dose and duration of use. Hormone therapy is not recommended in women with a history of endometrial cancer.<br>• Diagnosis of breast cancer increases with estrogen/progestogen therapy use beyond three to five years. It is not clear if the risk differs between continuous and sequential use of progesterone and if there is a class effect from the progesterone or whether the specific agent used influences breast cancer risk. In the WHI the increase in breast cancer was limited to those who had used estrogen/progestogen therapy before enrollment.<br>• Women in the estrogen therapy arm of the WHI demonstrated no |

| Clinical Guideline | Recommendation(s) |
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| | increase in risk of breast cancer after an average of 7.1 years of use. When estrogen therapy was extended beyond 10 to 15 years in observational studies, breast cancer risk seemed to increase.<br>• Controversy surrounds the safety of estrogen/progestogen therapy in survivors of breast cancer. Observational studies suggest that estrogen/progestogen therapy is safe and perhaps even protective against recurrence of breast cancer. However, these data have been questioned because of the potential bias from selection of women at low risk of recurrence using estrogen therapy.<br>• Published data on the role of hormone therapy and risk of ovarian cancer are conflicting. Most epidemiologic studies have shown no association or a modest increase. There is a relatively large volume of observational trial data that points to an association between hormone therapy use and increased ovarian cancer risk. In the WHI (the only randomized-controlled trial to date to study ovarian cancer), postmenopausal women taking daily continuous-combined estrogen/progestogen therapy for an average follow-up of 5.6 years did not exhibit a statistically significant increase in ovarian cancer. The association between ovarian cancer and hormone therapy beyond five years, if any, would fall into the rare or very rare category. Women at increased risk of ovarian cancer should be counseled about this rare association.<br>• The overall data, including the WHI analysis, suggest that initiating estrogen/progestogen therapy in older women with a history of smoking may promote the growth of existing lung cancers. However, evidence from the WHI and some case-control and cohort trials of hormone therapy in a younger population (<60 years) shows some protection against lung cancer. Findings reinforce the need to encourage prevention or cessation of smoking and possibly to increase surveillance in older smokers who are current or past users of hormone therapy.<br>• Although hormone therapy might have a positive effect on mood and behavior, hormone therapy is not an antidepressant and should not be considered as such. Evidence is insufficient to support its use for the treatment of depression.<br>• Hormone therapy cannot be recommended at any age for the sole or primary indication of preventing cognitive aging or dementia. Hormone therapy seems to increase the incidence of dementia when initiated in women ≥65 years of age. Similarly, hormone therapy should not be used to enhance cognitive function in younger postmenopausal women with intact ovaries, although very small clinical trials support the use of estrogen therapy initiated immediately after menopause induced by bilateral oophorectomy. Available data do not adequately address whether hormone therapy used soon after menopause increases or decreases later dementia risk. Limited data do not support the use of hormone therapy as treatment of Alzheimer's disease.<br>• There are inadequate data regarding hormone therapy in women experiencing premature menopause and premature ovarian insufficiency. Most observational reports suggest an increased risk of CHD with early natural or surgical menopause in the absence of hormone therapy and a protective effect of hormone therapy when hormone therapy is administered.<br>• The WHI trials are consistent with observational trials indicating that hormone therapy may reduce total mortality when initiated soon after menopause. |

| Clinical Guideline | Recommendation(s) |
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| | Practical therapeutic issues<br>• Estrogens and progestogens have some common features and effects as well as potentially different properties. In the absence of large-scale, rigorous, head-to-head randomized-controlled trials of various estrogens and progestogens, which are unlikely to be conducted, clinicians will be required to generalize the clinical trial results for one agent to all agents within the same hormonal family.<br>• The lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual women should be the therapeutic goal, with a corresponding low dose of progestogen added to counter the adverse effects of systemic estrogen therapy on the uterus. Lower estrogen therapy and estrogen/progestogen doses are better tolerated and may have a more favorable benefit-risk ratio compared to standard doses.<br>• There is currently no clear benefit of one route of administration vs another for systemic estrogen therapy. Systemic progestogen is required for endometrial protection from unopposed estrogen therapy. Topical transdermal progesterone delivery is not recommended when estrogen/progestogen therapy is prescribed. Intrauterine systems also cannot be recommended at this time.<br>• There are multiple dosing regimen options for endometrial safety when adding progestogen to estrogen. Research is inadequate to endorse one regimen over another. There are also multiple dosing regimen options from which to choose when using estrogen therapy alone for women after hysterectomy. No data provide guidance on which regimen is best for all women.<br>• Filled prescriptions for bioidentical hormone therapy should include a patient package insert identical to that required for products that have regulatory agency approval.<br><br>Treatment issues<br>• Hormone therapy should be considered only when an indication for therapy has been clearly identified, contraindications ruled out, and potential individual benefits and risk adequately discussed with each woman so that an informed decision can be made.<br>• Emerging data reveal that the timing of hormone therapy initiation in relation to proximity to menopause may be important. Women >60 years of age who experienced natural menopause at the median age and have never used hormone therapy will have elevated baseline risk of CHD, stroke, venous thromboembolism, and breast cancer, and hormone therapy should therefore not be initiated in this population without a compelling indication and only after appropriate counseling and attention to cardiovascular disease risk factors. Premature menopause and premature ovarian insufficiency are conditions associated with a lower risk of breast cancer and earlier onset of osteoporosis and CHD, but there are no clear data as to whether estrogen therapy or estrogen/progestogen therapy will affect morbidity or mortality from these conditions. Despite this, it is logical and considered safe to recommend hormone therapy for these younger women, at least until the median age of natural menopause. Younger women with premature menopause might also require higher doses of hormone therapy for menopause symptom relief compared to doses currently recommended for women 50 to 59 years of age.<br>• One of the most challenging issues regarding hormone therapy is the duration of use. Existing data do not provide a clear indication as to |

| Clinical Guideline | Recommendation(s) |
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| | whether longer duration of therapy improves or worsens the benefit-risk ratio. Treatment recommendations are different for women experiencing premature menopause, those who are first users of hormone therapy, or women who are in their 60s and have previously used hormone therapy for several years. Provided that the lowest effective dose is used, that the women is well aware of the potential benefits and risks, and that there is clinical supervision, extending hormone therapy use for an individual woman's treatment goals is acceptable under some circumstances, including:<br>○ The woman for whom, in her own opinion, the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop hormone therapy.<br>○ The women with established reduction in bone mass for whom alternate therapies are not appropriate or cause unacceptable side effects, or the benefit-risk ratio of extended use is unknown.<br>• Vasomotor symptoms have an approximately 50% chance of recurring when hormone therapy is discontinued, independent of age and duration of use. The decision to continue hormone therapy should be individualized on the basis of severity of symptoms and current benefit-risk ratio considerations, provided the woman in consultation with her healthcare provider believes that continuation of therapy is warranted.<br>• Current data suggest the rates of vasomotor symptom recurrence are similar when HT is either tapered or abruptly discontinued. No recommendation can be made as to how to discontinue therapy.<br>• An initial analysis of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results registries showed that the age-adjusted incidence rates of breast cancer in women in the United States fell sharply by 6.7% in 2003, as compared to the rate in 2002. The decrease was evident only in women who were ≥50 years of age and was more evident in cancers that were estrogen receptor positive compared to estrogen receptor negative. It was theorized that the drop could be related to the large number of women discontinuing hormone therapy after termination of the estrogen/progestogen therapy arm of the WHI. When followed for three years after stopping hormone therapy, women in the WHI who had been assigned to estrogen/progestogen therapy had a rate of cardiovascular events, fractures, and colon cancers equivalent to that of women who had been assigned placebo. The only statistical difference was an increase in the rates of all cancer in women who had been assigned to estrogen/progestogen therapy. Growing data indicate that discontinuance of hormone therapy will lead to expected complications such as increased incidence of bone fracture. Hazard ratios for all-cause mortality, reflecting the balance of all of the above and other outcomes, tended to be neutral for both estrogen/progestogen therapy and estrogen therapy arms of the WHI (0.98 and 1.04, respectively). During the three year postintervention phase of the estrogen/progestogen therapy trial, mortality rates were borderline elevated (1.15; 95% confidence interval [CI], 0.95 to 1.39) due primarily to the aforementioned increased in cancer. Over the entire estrogen/progestogen therapy follow-up period, the hazard ratio for all-cause mortality was 1.04 (95% CI, 0.91 to 1.18).<br>• An individual risk profile is essential for every woman contemplating any regimen of estrogen/progestogen therapy or estrogen therapy.<br>• Each woman is unique, having her own risk profile and preferences. |

| Clinical Guideline | Recommendation(s) |
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| | When hormone therapy is desired by patients, individualization of therapy is key to providing health benefits with minimal risks, thereby enhancing quality of life. |
| Practice Committee of the American Society for Reproductive Medicine: **Estrogen and Progestogen Therapy in Postmenopausal Women[50] (2008)** | • Hormone therapy reduces the number of hot flushes by approximately 18 per week more than placebo.<br>• The effect is greatest during the first year of treatment.<br>• There are no significant differences between the effects of different types of estrogen or routes of administration.<br>• Any influence of progestogen treatment, in continuous or cyclic forms, cannot be determined from the trial evidence. |
| European Menopause and Andropause Society (EMAS): **The EMAS 2008 Update on Clinical Recommendations on Postmenopausal Hormone Therapy[56] (2008)** | • The main indication for hormone therapy in postmenopausal women remains the relief of menopausal symptoms.<br>• Treatment significantly decreases bone loss and the risk of osteoporotic fractures.<br>• The risk of stroke is slightly increased by both estrogen-only and estrogen-progestin treatment, but remains of low clinical impact in women <70 years old.<br>• The risk of breast cancer increases according to the duration of treatment and is higher with estrogen-progestin than estrogen-only hormone therapy.<br>• For women ages 50 to 59 years, there may be a reduced risk of coronary heart disease with the use of hormone therapy; however, these findings are still controversial. |
| National Osteoporosis Foundation: **Clinician's Guide to Prevention and Treatment of Osteoporosis[57] (2010)** | Synopsis of major recommendations<br>• The following recommendations apply to postmenopausal women and men ≥50 years of age.<br>• Patients should be counseled on the risk of osteoporosis and related fractures.<br>• Secondary causes of osteoporosis should be assessed in patients.<br>• Patients should be advised to supplement with adequate amounts of calcium (≥1,200 mg/day) and vitamin D (800 to 1,000 international units [IU]/day), including supplements if necessary for patients ≥50 years of age.<br>• Regular weight-bearing and muscle-strengthening exercises should be recommended to reduce the risk of falls and fractures.<br>• Tobacco smoking and excessive alcohol intake should be avoided.<br>• Bone mineral density (BMD) testing is recommended in women ≥65 years of age and men ≥70 years of age.<br>• In postmenopausal women and men 50 to 69 years of age, recommend BMD testing when you have concern based on their risk factor profile.<br>• A BMD test is recommended to those who have had a fracture, in order to determine the degree of disease severity.<br>• Treatment should be initiated in patients with hip or vertebral (clinical or morphometric) fractures.<br>• Initiate therapy in those patients with BMD T-scores ≤-2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry, after appropriate evaluation.<br>• Initiate treatment in postmenopausal women and men ≥50 years of age with low bone mass (T-score -1.0 to -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on the Untied States-adapted World Health Organization absolute fracture risk model.<br>• Current Food and Drug Administration (FDA)-approved pharmacologic options for osteoporosis prevention and/or treatment |

| Clinical Guideline | Recommendation(s) |
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| | are bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, and parathyroid hormone (teriparatide).<br>• BMD testing performed in dual-energy x-ray absorptiometry centers using accepted quality assurance measures is appropriate for monitoring bone loss. For patients on pharmacotherapy, it is typically performed two years after initiating therapy and every two years thereafter; however, more frequent testing may be warranted in certain clinical solutions. |
| North American Menopause Society (NAMS):<br>**The Role of Local Vaginal Estrogen for Treatment of Vaginal Atrophy in Postmenopausal Women: 2007 Position Statement[47] (2007)** | • Nonhormonal vaginal lubricants and moisturizers should be considered as first-line therapies for women with vaginal atrophy.<br>• All low-dose vaginal estrogen products, approved in the United States for the treatment of vaginal atrophy, are equally effective at the recommended doses from product labeling.<br>• Management of vaginal atrophy is similar between women with non-hormone-dependent cancer and women without a cancer history.<br>• Clinical judgment and patient preference should guide the choice of therapy selected. |
| American Heart Association (AHA):<br>**Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women[51] (2007)** | • Hormone therapy should not be used for the primary or secondary prevention of cardiovascular diseases.<br>• Other approaches such as lowering cholesterol and controlling blood pressure should be considered for cardiovascular disease prevention. |
| International Menopause Society (IMS):<br>**IMS Updated Recommendations on Postmenopausal Hormone Therapy and Preventive Strategies for Midlife Health[58] (2011)** | Hormonal therapy<br>• Hormone replacement therapy is effective in preventing the bone loss associated with menopause or secondary amenorrhea.<br>• Even in women not a high risk of fracture, hormone replacement therapy decreases in the incidence of all osteoporosis-related fractures, including vertebral and hip fractures.<br>• Hormone replacement therapy is one of the first-line choices of therapy in postmenopausal women 50 to 60 years of age presenting with a substantial risk of fracture.<br>• The rate at which the protective effect of hormone replacement therapy on bone mineral density is lost after cessation of therapy is unpredictable. Although some degree of fracture protection may remain after cessation of therapy, high risk patients for fracture may be a candidate for additional therapy with proven bone-sparing medication.<br>• The continuation of HRT in patients >60 years of age for the sole purpose of the prevention of fractures should take into account possible adverse events of the specific dose and method of administration of HRT, compared to other proven therapies.<br>• The initiation of HRT for the sole purpose of the prevention of fractures is not recommended after 60 years of age. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause[37] (2011)** | • Menopausal hormone therapy may be appropriate for the relief of severe menopausal symptoms in selected postmenopausal women, on the basis of individually determined benefit-vs-risk prolife.<br>• Menopausal hormone therapy may be prescribed during the perimenopause and early menopause for relief of menopausal symptoms and treatment of vulvovaginal atrophy.<br>• The use of the transdermal route of estrogen administration should be considered in order to avoid the hepatic "first-pass effect," which may theoretically reduce the risk of thromboembolic disease.<br>• The use of transvaginal estrogen may be considered to provide topical effects with less systemic absorption. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • The dose of menopausal hormone therapy may be reduced with advancing age.<br>• Because of the increased risk of endometrial cancer, unopposed estrogen should not be used in women with an intact uterus.<br>• Progestational agents should be used for a minimum of 10 to 14 days per month in women treated with estrogen who have an intact uterus.<br>• Long-cycle therapy with use of a progestogen for 14 days every three months may be considered, in an effort to reduce breast exposure to progestogens, despite lack of definitive assessment of efficacy.<br>• Amenorrhea may be achieved by using a low dose of progestogen administered continuously (daily) in conjunction with estrogen. Because recent trials suggest adverse breast outcomes with continuous progesterone exposure, this form of therapy is not recommended.<br>• Menopausal hormone therapy should be used in the lowest dose and for the shortest period necessary to control menopausal symptoms.<br>• Therapeutic trials of nonhormonal prescription medications (e.g., clonidine, antidepressants, gabapentin) may also be considered for the relief of menopausal symptoms in women with no specific contraindications.<br>• Over-the-counter supplements should be used with caution because they are not regulated by the United States FDA and have the potential for interactions with drugs and for causing harm.<br>• Phytoestrogens, including soy-derived isoflavonoids, result in inconsistent relief of symptoms. Because these compounds may have estrogenic effects, women with a personal or strong family history of hormone-dependent cancers, thromboembolic events, or cardiovascular events should not use soy-based therapies.<br>• Custom compounded “biochemical hormone therapy” is not recommended.<br>• FDA-approved bioidentical hormone preparations may be considered, but evidence is lacking that they are safer or more effective compared to traditional forms of hormone therapy.<br>• Menopausal hormone therapy should be used for the prevention and treatment of osteoporosis within the context of the overall benefit-vs-risk analysis of each patient. Data from multiple randomized-controlled trials substantiate the efficacy of estrogens in preserving bone mass, and less consistently, preventing fractures, but nonhormonal therapeutic options for bone health exist.<br>• Hormone therapy for the prevention or treatment (or both) of dementia is not recommended.<br>• Menopausal hormone therapy should be prescribed to women in conjunction with a thorough discussion of the possible relationship of menopausal hormone therapy to breast cancer. Current evidence suggests that estrogen/progestogen regimens are associated with a possible higher risk of breast cancer compared to estrogen therapy.<br>• Concordant with current FDA warnings, it is recommended that women who are at increased risk of thromboembolic disease should not take estrogen-containing therapy.<br>• Women should be advised that smoking increases the risk of cardiovascular and venous thromboembolic disease when taking estrogen, and aggressive smoking cessation programs should be advised.<br>• Menopausal hormone therapy is not recommended for primary or secondary prevention of cardiovascular disease.<br>• Lipid profiles, smoking history, and diabetes as well as family history |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | should be assessed to assist in the determination of individual cardiovascular risk.<br>• Women should be advised that cerebrovascular accidents occur with increased frequency in patients with estrogen alone or estrogen/progesterone therapy in an age-dependent manner.<br>• Women should be advised that there may be an increase in ovarian epithelial tumors with the use of estrogen for more than ten years.<br>• Women may be advised that several trials, including the WHI, have demonstrated a lower risk of colon cancer in women treated with estrogen/progesterone therapy.<br>• The FDA has approved the use of menopausal hormone therapy for the following:<br>  ○ Treatment of moderate to severe vasomotor symptoms associated with menopause. Estrogen-containing products are the most effective approved therapies for these symptoms.<br>  ○ Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. When estrogen is prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal preparations should be considered.<br>• Prevention of postmenopausal osteoporosis. When menopausal hormone therapy is being prescribed solely for the prevention of postmenopausal osteoporosis, approved non-estrogen treatments should be carefully considered. Estrogen therapy and estrogen/progesterone therapy should be considered only in women with substantial risk of osteoporosis that outweighs the potential drug-related risks. |
| Agency for Healthcare Research and Quality (AHRQ), United States Preventive Services Task Force (USPSTF):<br>**Hormone Therapy for the Prevention of Chronic Conditions in Postmenopausal Women[52] (2005)** | • For most women, the possible harmful effects of combined estrogen and progestin are likely to exceed possible benefits in chronic disease prevention.<br>• For most women, the possible harmful effects of unopposed estrogen are likely to exceed possible benefits in chronic disease prevention.<br>• Estrogen is not recommended to prevent chronic health conditions in postmenopausal women who have had a hysterectomy.<br>• The United States Preventive Services Task Force does not make any recommendations on the use of hormone therapy for the management of menopausal symptoms. Women and their clinicians are encouraged to discuss the risks and benefits of using hormone replacement therapy for menopausal symptoms. |
| National Institutes of Health (NIH):<br>**Consensus and State-of-the-Science Conference Statement on Management of Menopause-Related Symptoms[53] (2005)** | • Estrogen, alone or with progestins, is the most effective treatment for hot flashes and night sweats.<br>• Estrogen therapy increases the risk for stroke, deep venous thrombosis, pulmonary embolism, coronary events, and breast cancer.<br>• For women with severe menopausal vasomotor symptoms, the decision to use HRT would require balancing the potential benefits against the potential risks. |
| American College of Obstetricians and Gynecologists (ACOG)Task Force on Hormone Therapy/American College of Obstetricians and Gynecologists Women's Health Care Physicians:<br>**Summary of Balancing Risks** | • Hormone therapy is not recommended for the prevention of chronic diseases in postmenopausal women. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **and Benefits[38] (2004)** | |
| Royal College of Obstetricians and Gynaecologists (RCOG): **Venous Thromboembolism and Hormone Replacement Therapy[36] (2011)** | • The mechanism by which oral hormone replacement therapy provokes an increased risk of venous thromboembolism (VTE) is unclear.<br>• Women initiating hormone replacement therapy should be counseled about the risk of VTE and the signs and symptoms of VTE.<br>• Women should be advised to immediately seek medical help if they suspect that they have developed a thrombosis.<br>• Women initiating or continuing hormone replacement therapy should be counseled on the perceived benefits and possible risks for their individual situations, including consideration of alternative therapies.<br>• The risks of VTE in association with hormone replacement therapy may be influenced by the type of preparation and the duration of its use.<br>• The risk of VTE may be less with esterified estrogens compared with conjugated equine estrogen.<br>• There may be a greater risk of VTE with combination therapy and definitive information on individual estrogen types is still lacking. However, the results to date suggest that therapy with estrogen alone is associated with a significant VTE risk.<br>• There is some evidence that the effect of estrogen therapy may be dose related.<br>• Transdermal preparations are associated with a substantially lower risk of VTE compared to oral preparations.<br>• The risk of VTE is highest in the first year of hormone replacement therapy, with no evidence of continuing risk on stopping hormone replacement therapy.<br>• Universal screening of women for thrombophilic defects before prescribing or before continuing the prescription of hormone replacement therapy is inappropriate.<br>• Oral hormone replacement therapy should be avoided in women without a personal history of VTE but with a high-risk thrombophilic trait that has been identified through screening because of a symptomatic family member.<br>• A personal history of thrombosis is a contraindication to oral hormone replacement therapy.<br>• If it is considered that quality of life is so severely affected that the benefits of hormone replacement therapy outweigh the risks, a transdermal preparation should be used.<br>• It is recommended that hormone replacement therapy be discontinued when a women receiving therapy develops a VTE.<br>• If it is considered desirable that a woman should continue hormone replacement therapy after a VTE has occurred on therapy, she should be referred to a clinician with special expertise in managing women at increased thrombotic risk requiring hormone replacement therapy.<br>• Before initiating hormone replacement therapy, any personal or family history of VTE should be assessed.<br>• A history of VTE in a first-degree relative is a relative contraindication to hormone replacement therapy.<br>• When there is a family history of VTE in a first-degree relative, alternatives to oral hormone replacement therapy should be suggested. If hormone replacement therapy is considered desirable, transdermal preparations are associated with a significantly lower risk of venous thrombosis.<br>• Hormone replacement therapy should be avoided in women with multiple pre-existing risk factors for VTE. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • An individual assessment of the risks and benefits of stopping hormone replacement therapy before elective surgery is required for all women. Hormone replacement therapy may not need to be discontinued prior to surgery provided that appropriate thromboprophylaxis is utilized. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the estrogens are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Estrogens-Single Entity Products[2-24]**

| Indications | Estradiol | Estradiol Acetate | Estradiol Cypionate | Estradiol Valerate | Estrogens, Conjugated Equine | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified | Estropipate |
|---|---|---|---|---|---|---|---|---|---|
| Palliative treatment of advanced prostate cancer | ✔ (Estrace®*) | | | ✔ | ✔ * | | | ✔ | |
| Palliative treatment of metastatic breast cancer | ✔ (Estrace®*) | | | | ✔ * | | | ✔ | |
| Prevention of postmenopausal osteoporosis | ✔ (Alora®, Climara®, Estrace®*, Menostar®, Vivelle-Dot®) | | | | ✔ * | | | | |
| Prevention of osteoporosis | | | | | | | | | ✔ |
| Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology | | | | | ✔ † | | | | |
| Treatment of atrophic vaginitis and kraurosis vulvae | | | | | ✔ ‡ | | | | |
| Treatment of hypoestrogenis | ✔ (Alora®, | | ✔ | ✔ | ✔ * | | | ✔ | ✔ |

| Indications | Estradiol | Estradiol Acetate | Estradiol Cypionate | Estradiol Valerate | Estrogens, Conjugated Equine | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified | Estropipate |
|---|---|---|---|---|---|---|---|---|---|
| m due to hypogonadism, castration, or primary ovarian failure | Climara®, Estrace®*, Vivelle-Dot®) | | | | | | | | |
| Treatment of vasomotor symptoms associated with menopause | ✔ (Alora®, Climara®, Divigel®, Elestrin®, Estrace®*, Estrasorb®, Evamist®, Vivelle-Dot®) | ✔ | ✔ | ✔ | ✔ * | ✔ | ✔ | ✔ | ✔ |
| Treatment of vulvar and vaginal atrophy associated with menopause | ✔ (Alora®, Climara®, Estrace®*, Estring®, Vagifem®, Vivelle-Dot®) | ✔ § | | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Treatment of vulvar and vaginal atrophy | ✔ (Estrace®‡) | | | | | | | | |

*Tablet formulation.
†Injection formulation.
‡Cream formulation.
§Vaginal ring formulation

**Table 4. FDA-Approved Indications for the Estrogens-Combination Products[25-34]**

| Indications | Estradiol and Drospirenone | Estradiol and Levonorgestrel | Estradiol and Norethindrone | Estradiol and Norgestimate | Estrogen, Conjugated Equine and Medroxyprogesterone | Ethinyl Estradiol and Norethindrone |
|---|---|---|---|---|---|---|
| Prevention of postmenopausal osteoporosis | | ✔ | ✔ (Activella®) | ✔ | ✔ | ✔ |
| Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure | | | ✔ (Combipatch®) | | | |
| Treatment of moderate to severe symptoms of vulvar | ✔ (1/0.5 mg) | | ✔ | ✔ | ✔ | |

| Indications | Estradiol and Drospirenone | Estradiol and Levonorgestrel | Estradiol and Norethindrone | Estradiol and Norgestimate | Estrogen, Conjugated Equine and Medroxyprogesterone | Ethinyl Estradiol and Norethindrone |
|---|---|---|---|---|---|---|
| and vaginal atrophy due to menopause | | | | | | |
| Treatment of moderate to severe vasomotor symptoms due to menopause | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the estrogens are listed in Table 5.

**Table 5. Pharmacokinetic Parameters of the Estrogens[1]**

| Generic Name(s) | Bioavailability | Protein Binding | Metabolism | Excretion | Half-Life |
|---|---|---|---|---|---|
| **Single Entity Agents** | | | | | |
| Estradiol | Transdermal: 20 times higher bioavailability compared to oral dosage forms<br><br>Vaginal ring: 8%. | Primarily bound to SHBG and to albumin | Liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine) | Transdermal (gel):<br>Divigel®: 10 hours<br>Estrogel®: 36 hours<br><br>Transdermal (patch):<br>Alora®:1.75 hours<br>Vivelle®: 4.4 hours<br>Vivelle-Dot®: 5.9 to 7.7 hours |
| Estradiol acetate | Oral: rapidly absorbed<br><br>Vaginal: rapidly absorbed for the first hour, followed by a decline to constant rate for the remaining three months | Primarily bound to SHBG and to albumin | Liver (primary). Estradiol, estrone, and estriol are all active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine) | Not reported |
| Estradiol cypionate | Intramuscular: absorbed over several weeks | Primarily bound to SHBG and to albumin | Liver (primary). Estrone and estriol are both active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary | Not reported |

| Generic Name(s) | Bioavailability | Protein Binding | Metabolism | Excretion | Half-Life |
|---|---|---|---|---|---|
| | | | | secretion of conjugates into the intestine, hydrolyzed, and reabsorbed) | |
| Estradiol valerate | Intramuscular: absorbed over several weeks | Primarily bound to SHBG and to albumin | Liver (primary). Estrone and estriol are both active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine, hydrolyzed, and reabsorbed) | Not reported |
| Estrogens, Conjugated Equine | Oral: well absorbed | Bound to albumin, SHBG, cortisol binding globulin, and α-1-glycoproteins | Liver (primary). Estradiol, estrone, and estriol are all active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine) | Oral (estrone): 26.5 to 26.7 hours |
| Estrogens, conjugated, synthetic A | Well absorbed | Primarily bound to SHBG and to albumin | Liver (primary). Estradiol, estrone, and estriol are all active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine) | 10.6 hours (baseline-corrected estrone) |
| Estrogens, conjugated, synthetic B | Well absorbed | Primarily bound to SHBG and to albumin | Liver (primary). Estradiol, estrone, and estriol are all active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) | 14.26 hours (baseline-corrected estrone) |

| Generic Name(s) | Bioavailability | Protein Binding | Metabolism | Excretion | Half-Life |
|---|---|---|---|---|---|
| | | | | and bile (biliary secretion of conjugates into the intestine) | |
| Estrogens, esterified | Not reported | Primarily bound to SHBG and to albumin | Liver (primary). Estradiol, estrone, and estriol are all active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine) | Not reported |
| Estropipate | Well absorbed | Primarily bound to SHBG and to albumin | Liver (primary). Estradiol, estrone, and estriol are all active metabolites | Urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine) | Not reported |
| **Combination Products** | | | | | |
| Estradiol and drospirenone | Drospirenone: 76 to 85%<br><br>Estradiol: 53% | Drospirenone: 97% bound to serum proteins<br><br>Estradiol: primarily bound to SHBG and to albumin | Drospirenone: liver (extensive) and cytochrome P450 3A4 isoenzyme (minor). No active metabolites<br><br>Estradiol: liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolite | Drospirenone: urine (38 to 47% as glucuronide and sulfate conjugates) and feces (17 to 20% as glucuronide and sulfate conjugates)<br><br>Estradiol: urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of | Drospirenone: 36 to 42 hours<br><br>Estradiol: not reported |

| Generic Name(s) | Bioavailability | Protein Binding | Metabolism | Excretion | Half-Life |
|---|---|---|---|---|---|
| | | | | conjugates into the intestine) | |
| Estradiol and levonorgestrel | Estradiol (transdermal): 20 times higher bioavailability compared to oral dosage forms<br><br>Levonorgestrel: not reported | Estradiol: primarily bound to SHBG and to albumin<br><br>Levonorgestrel: bound to SHBG and to albumin (97.5 to 99%) | Estradiol: liver (primary) and skin (minimal). Estradiol, estrone, and estriol are all active metabolites<br><br>Levonorgestrel: blood (extent unspecified). Activity of three metabolites not specified | Estradiol: urine (estradiol, estrone, and estriol along with glucuronide and sulfate conjugates) and bile (biliary secretion of conjugates into the intestine)<br><br>Levonorgestrel: urine (45% of levonorgestrel and metabolites are excreted in the urine, mostly as glucuronide conjugates) and feces (32% of levonorgestrel and metabolites are excreted in the urine, mostly as glucuronide conjugates) | Estradiol: 1.75 to 77 hours<br><br>Levonorgestrel: Not reported |
| Estradiol and norethindrone | Estradiol (oral): 53%<br><br>Norethindrone (oral): 100% | Estradiol (oral): SHBG (37%), albumin (61%), and unbound (1 to 2 %)<br><br>Norethindrone: SHBG (36%) and albumin (61%) | Estradiol (oral): liver (primary)<br><br>Norethindrone: liver (primary) | Estradiol (oral): urine (metabolites as glucuronide and sulfate conjugates<br><br>Norethindrone (oral): liver (primary). | Estradiol (oral): 12 to 14/8 to 11 hours<br><br>Norethindrone (transdermal): 2 to 3 hours |
| Estradiol and norgestimate | Not reported | Estradiol: primarily bound to SHBG and to albumin<br><br>Norgestimate (17-deacetyl- | Estradiol: liver (primary). Estradiol, estrone, and estriol are all active metabolites | Estradiol: urine (estradiol, estrone, estriol, and glucuronide and | Estradiol: 16 hours<br><br>Norgestimate (17-deacetyl-norgestimate): |

| Generic Name(s) | Bioavailability | Protein Binding | Metabolism | Excretion | Half-Life |
|---|---|---|---|---|---|
| | | norgestimate): primarily bound to serum proteins (99%) | Norgestimate: liver (extensive) and gastrointestinal tract (extensive). 17-deacetylnoregestimate is an active metabolite | sulfate conjugates)<br><br>Norgestimate: urine and feces | 37 hours |
| Estrogen, conjugated equine and medroxyprogesterone | Well absorbed | Estrogen, conjugated: largely bound to SHBG and albumin<br><br>Medroxyprogesterone: primarily bound to plasma proteins (99%) | Estrogen, conjugated: liver (primary). Estradiol, estrone, and estriol are all active metabolites<br><br>Medroxyprogesterone: liver (primary) | Estrogen, conjugated: urine (estradiol, estrone, estriol, and glucuronide and sulfate conjugates<br><br>Medroxy-progesterone urine (most metabolites excreted as glucuronide conjugates with only minor amounts excreted as sulfates) | Estrogen, conjugated: (estrone): 20.7 to 23.6 hours<br><br>Medroxyprogesterone: 26.2 to 46.3 hours |
| Ethinyl estradiol and norethindrone | Ethinyl estradiol: 55%<br><br>Norethindrone: 64% | Ethinyl estradiol: largely bound to albumin (>95%)<br><br>Norethindrone: largely bound to albumin and SHBG (>95%) | Ethinyl estradiol: liver (primary)<br><br>Norethindrone acetate: liver (primary) | Ethinyl estradiol: urine and feces (primarily as metabolites)<br><br>Norethindrone: urine and feces (primarily as metabolites) | Ethinyl estradiol: 24 hours<br><br>Norethindrone: 13 hours |

SHBG=sex hormone binding globulin

## V. Drug Interactions

Significant drug interactions with the estrogens are listed in Table 6.

**Table 6. Significant Drug Interactions with the Estrogens[59]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Estrogens (conjugated estrogens, esterified estrogens, estradiol, estropipate, ethinyl estradiol) | 1 | Bosentan | Bosentan induces cytochrome P450 3A4 and 2C9 isoenzymes which may lead to a decrease in the effectiveness of estrogens. |
| Estrogens (conjugated estrogens, esterified estrogens, estradiol, estrone, estropipate, ethinyl estradiol) | 2 | Barbiturates | Barbiturates induce the hepatic microsomal enzymes and may increase the elimination of estrogens and decrease plasma concentrations. |
| Estrogens (conjugated estrogens, esterified estrogens, estradiol, estrone, estropipate, ethinyl estradiol) | 2 | Corticosteroids | Estrogens inactivate the hepatic cytochrome P450 which may result in an increase in the effects of corticosteroids. |
| Estrogens (conjugated estrogens, esterified estrogens, estradiol, estrone, estropipate) | 2 | Hydantoins | Hydantoins induce hepatic enzymes that may increase metabolism of estrogens. Protein binding of phenytoin may be affected. |
| Estrogens (conjugated estrogen, esterified estrogens, estradiol, estrone, estropipate, ethinyl estradiol) | 2 | Rifamycins | Rifamycins induce the cytochrome P450 3A4 isoenzymes. Coadministration may reduce plasma concentrations of estrogens. This may result in a decrease of therapeutic effects and/or changes in the uterine bleeding profile. |
| Estrogens (conjugated estrogens, esterified estrogens, estradiol, estropipate, ethinyl estradiol) | 2 | Thyroid hormones | Estrogens may increase serum thyroxine-binding globulin concentrations and therefore change serum thyroxine and thyrotropin concentrations. Thyroid hormone requirements may increase. |
| Estrogens (conjugated estrogens, esterified estrogens, estradiol, estrone, estropipate, ethinyl estradiol) | 2 | Topiramate | Topiramate may increase the metabolism of estrogens and therefore decrease their efficacy. |
| Ethinyl estradiol | 2 | Modafinil | Modafinil may induce gastrointestinal (major) and hepatic (minor) metabolism of ethinyl estradiol and impair efficacy. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

The most common adverse drug events reported with the estrogens are listed in Tables 7 and 8. The boxed warning for the estrogens is listed in Table 9.

**Table 7. Adverse Drug Events (%) Reported with the Estrogens-Single Entity Agents[2-24]**

| Adverse Event | Estradiol | Estradiol Acetate | Estradiol Cypionate* | Estradiol Valerate* | Estrogens, Conjugated Equine* | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified* | Estrop-ipate† |
|---|---|---|---|---|---|---|---|---|---|
| **Breasts** | | | | | | | | | |
| Breast cancer | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Enlargement | 1.1 to 6.7 (Alora®) | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Fibrocystic breast changes | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Galactorrhea | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Neoplasm | 1.1 to 5.6 (Alora®) | - | - | - | - | - | - | - | - |
| Nipple discharge | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Nipple pain | 1 to 7 (Evamist®) | - | - | - | - | - | - | - | - |
| Pain | 6.9 to 34.8 (Alora®)/5.0 to 29.0 (Climara®)/10.0 (Estrasorb®)/1.0 (Estring®)/5.0 (Menostar®) | - | ✔ | ✔ | ✔ (injection)/ 7.0 to 11.0 (tablet)/ 2.1 to 4.9 (vaginal cream) | 29 | 0 to 14 | ✔ | - |
| Tenderness | 2.5 to 8.8 (Divigel®)/6.6 to 7.7 (Elestrin®)/5.0 to 7.0 (Evamist®)/6.5 to 17.0 (Vivelle-Dot®) | 0 to 6.3 (tablet)/6.2 to 10.7 (vaginal ring) | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| **Cardiovascular** | | | | | | | | | |
| Cardiovascular | 10 (Menostar®) | - | - | - | - | - | - | - | - |
| Chest pain | 1.1 to 4.5 (Alora®)/1.0 to 3.0 (Estring®) | - | - | - | - | - | - | - | - |
| Deep and superficial venous thrombosis | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Increase in blood pressure | 0.0 to 6.7 (Alora®)/0.0 to 4.3 (Vivelle-Dot®) | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Myocardial infarction | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Palpitation | - | - | - | - | - | 5.7 to 21.0 | - | - | - |
| Pulmonary embolism | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Stroke | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Syncope | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Thrombophlebitis | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Vasodilation | 0 to 6.7 (Alora®) | - | - | - | 2.8 to 2.9 (vaginal cream) | 3.8 | - | - | - |
| **Central Nervous System** | | | | | | | | | |
| Anxiety | 0 to 10.0 (Alora®)/1.0 to 3.0 (Estring®)/1.5 to 6.4 (Vivelle-Dot®) | - | - | - | - | 5.7 | - | - | - |
| Asthenia | 0 to 7.9 (Alora®) | - | - | - | 7 to 8 (tablet) | 11.3 to 33.0 | - | - | - |
| Chorea | - | - | ✔ | ✔ | - | - | - | ✔ | ✔ |
| Dementia | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Depression | 1.1 to 3.4 (Alora®)/1.0 to 8.0 (Climara®)/3.0 to 10.6 (Vivelle-Dot®) | - | ✔ | ✔ | ✔ (injection)/ | 3.8 to 28.0 | - | ✔ | ✔ |

| Adverse Event | Estradiol | Estradiol Acetate | Estradiol Cypionate* | Estradiol Valerate* | Estrogens, Conjugated Equine* | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified* | Estrop-ipate† |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 5 to 8 (tablet) | | | | |
| Dizziness | 0.6 to 7.8 (Alora®)/5.0 (Menostar®) | - | ✔ | ✔ | ✔ (injection)/ 4 to 6 (tablet) | 11 | 1 to 7 | ✔ | ✔ |
| Exacerbation of chorea | - | - | - | - | ✔ (injection) | - | - | - | - |
| Exacerbation of epilepsy | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Headache | 5.6 to 21.3 (Alora®)/15.0 to 18.0 (Climara®)/9.0 (Estrasorb®)/13.0 (Estring®)/1.0 to 12.0 (Evamist®)/9.0 (Vagifem®)/14.9 to 50.0 (Vivelle-Dot®) | 3.0 to 4.2 (tablet)/7.1 to 9.8 (vaginal ring) | ✔ | ✔ | ✔ (injection)/ 26 to 32 (tablet)/ 2.1 to 3.5 (vaginal cream) | 11.3 to 68.0 | 15 to 25 | ✔ | ✔ |
| Hypertonia | - | - | - | - | - | 6 | - | - | - |
| Hypesthesia | 0 to 3.4 (Alora®) | - | - | - | - | - | - | - | - |
| Insomnia | 1.1 to 4.6 (Alora®)/4.0 (Estring®)/1.5 to 6.4 (Vivelle-Dot®) | - | - | - | 6 to 7 (tablet) | 5.7 to 42.0 | - | - | - |
| Irritability | - | - | ✔ | ✔ | - | - | - | ✔ | - |
| Migraine | 0 to 6.7 (Alora®)/1.0 to 3.0 (Estring®) | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Mood disturbances | - | - | ✔ | ✔ | - | - | - | ✔ | - |
| Nervousness | - | - | ✔ | ✔ | ✔ (injection)/ 2 to 5 (tablet) | 3.8 to 28.0 | - | ✔ | - |
| Paresthesia | - | - | - | - | - | 7.5 to 33.0 | 0 to 6 | - | - |
| Possible growth potentiation of benign meningioma | | | - | - | ✔ (injection) | | | | |
| Vertigo | - | - | - | - | - | 5.7 to 17.0 | - | - | - |
| **Eyes** | | | | | | | | | |
| Conjunctivitis | 0 to 3.3 (Alora®) | - | - | - | - | - | - | - | - |
| Intolerance to contact lenses | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Retinal vascular thrombosis | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | |
| Steepening of corneal curvature | - | - | ✔ | - | - | - | - | ✔ | ✔ |
| **Gastrointestinal** | | | | | | | | | |
| Abdominal cramps | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Abdominal distention | - | 2.7 to 7.1 (vaginal ring) | - | - | - | - | - | - | - |
| Abdominal pain | 1.1 to 7.9 (Alora®)/0 to 16.0 (Climara®)/4.0 (Estring®)/8.0 (Menostar®)/7.0 (Vagifem®) | 0 to 3.2 (tablet) | - | - | 15 to 17 (tablet) | 9.4 to 28.0 | 4 to 15 | - | - |
| Bloating | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Cholestatic jaundice | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Constipation | 1.1 to 6.7 (Alora®)/5.0 (Menostar®)/1.5 to 6.5 (Vivelle-Dot®) | - | - | - | - | 6 | - | - | - |
| Diarrhea | 1.1 to 3.3 (Alora®)/1 to 3 (Estring®)/5 (Vagifem®) | - | - | - | 6 to 7 (tablet) | 6 | - | - | - |
| Dyspepsia | 1.1 to 9.0 (Alora®)/1.0 to 3.0 (Estring®)/5.0 (Menostar®)/2.9 to 9.2 (Vivelle-Dot®) | - | - | - | 9 to 11 (tablet) | 10 | - | - | - |
| Enlargement of hepatic hemangiomas | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |

| Adverse Event | Estradiol | Estradiol Acetate | Estradiol Cypionate* | Estradiol Valerate* | Estrogens, Conjugated Equine* | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified* | Estrop-ipate† |
|---|---|---|---|---|---|---|---|---|---|
| Flatulence | 1.1 to 4.6 (Alora®)/1 to 7 (Climara®)/1 to 3 (Estring®) | - | - | - | 6 to 7 (tablet) | 29 | 4 to 7 | - | - |
| Gastritis | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Gastroenteritis | 0 to 4.4 (Alora®) | - | - | - | - | - | - | - | - |
| Increased incidence of gallbladder disease | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Ischemic colitis | - | - | - | - | ✔ (injection) | - | - | - | - |
| Nausea | 3.4 to 6.7 (Alora®)/1.0 to 6.0 (Climara®)/3.0 (Estring®)/1.0 to 3.0 (Evamist®)/3.9 to 6.2 (Vivelle-Dot®) | 0 to 2.3 (tablet)/ 1.8 to 2.7 (vaginal ring) | ✔ | ✔ | ✔ (injection)/ 6 to 9 (tablet) | 9.4 to 18.0 | 7 to 12 | ✔ | ✔ |
| Pancreatitis | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Vomiting | - | - | - | - | ✔ (injection) | 7 | - | ✔ | ✔ |
| **Genitourinary System** | | | | | | | | | |
| Asymptomatic genital bacterial growth | 4 (Estring®) | - | - | - | - | - | - | - | - |
| Breakthrough bleeding | - | - | ✔ | ✔ | - | - | - | - | ✔ |
| Cervical polyps | 6 (Menostar®) | - | - | - | - | - | - | - | - |
| Change in amount of cervical secretion | - | - | ✔ | ✔ | - | - | - | - | ✔ |
| Changes in cervical ectropion | | | ✔ | ✔ | | | | | |
| Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow | - | - | ✔ | ✔ | - | - | - | - | ✔ |
| Cystitis | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Dysmenorrhea | 0 to 6.5 (Vivelle-Dot®) | - | ✔ | ✔ | - | 6 | 1 to 8 | - | - |
| Dysuria | 1 to 3 (Estring®) | - | - | - | 1.4 (vaginal cream) | - | - | - | - |
| Endometrial cancer | | | ✔ | ✔ | | | | | |
| Endometrial disorder | 15 (Estrasorb®) | - | - | - | - | - | - | - | - |
| Endometrial hyperplasia | | | ✔ | ✔ | | | | | |
| Endometrial thickening | - | - | - | - | - | 18.9 | - | - | - |
| Genital eruption | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Increase in size of uterine leiomyomata | - | - | ✔ | ✔ | - | - | - | - | ✔ |
| Intermenstrual bleeding | 0 to 10.6 (Vivelle-Dot®) | 0 to 3.2 (tablet) / 8.0 to 9.8 (vaginal ring) | - | - | - | - | - | - | - |
| Leukorrhea | 1.7 to 4.5 (Alora®)/1.0 to 7.0 (Climara®)/7.0 (Estring®)/11.0 (Menostar®) | - | - | - | 4.0 to 7.0 (tablet)/2.1 to 2.9 (vaginal cream) | - | - | - | - |
| Menorrhagia | - | - | - | - | - | 14 | - | - | - |

| Adverse Event | Estradiol | Estradiol Acetate | Estradiol Cypionate* | Estradiol Valerate* | Estrogens, Conjugated Equine* | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified* | Estrop-ipate† |
|---|---|---|---|---|---|---|---|---|---|
| Metorrhagia | 4.1 to 9.6 (Divigel®)/4.4 to 9.2 (Elestrin®) | - | - | - | - | - | - | - | - |
| Ovarian cancer | | | ✔ | ✔ | | | | | |
| Spotting | - | - | ✔ | ✔ | - | - | - | - | ✔ |
| Urinary incontinence | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Urinary tract infection | 1.7 to 5.6 (Alora®)/2.0 (Estring®) | 0.9 to 3.6 (vaginal ring) | - | - | - | - | - | - | - |
| Urogenital pruritis | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Uterine pain | - | 1.8 to 4.5 (vaginal ring) | - | - | - | - | - | - | - |
| Vaginal bleeding | 8.7 to 33.3 (Alora®) | 0.8 to 7.4 (tablet) | - | - | - | - | - | - | - |
| Vaginal candidiasis | - | 6.2 to 10.7 (vaginal ring) | - | - | - | - | - | - | ✔ |
| Vaginal discharge | - | 2.3 to 4.0 (tablet)/ 1.8 to 2.7 (vaginal ring) | - | - | - | - | - | - | - |
| Vaginal hemorrhage | 4 (Estring®) | - | - | - | 2.0 to 14.0 (tablet)/0.7 to 1.4 (vaginal cream) | - | - | - | - |
| Vaginal irritation | - | 0.9 to 1.8 (vaginal ring) | - | - | - | - | - | - | - |
| Vaginal moniliasis | - | - | - | - | 5.0 to 6.0 (tablet)/1.4 (vaginal cream) | - | - | - | - |
| Vaginal mycosis | 2.4 to 6.4 (Divigel®) | - | - | - | - | - | - | - | - |
| Vaginal pain/discomfort | 5 (Estring®) | - | - | - | - | - | - | - | - |
| Vaginitis | 0 to 8.0 (Alora®)/5.0 (Estring®) | - | - | - | 5.0 to 7.0 (tablet)/1.4 to 2.1 (vaginal cream) | 7.5 | 2 to 7 | - | - |
| Vulvovaginal disorder | - | - | - | - | 2.1 to 2.8 (vaginal cream) | - | - | - | - |
| Vulvovaginal mycotic infection | 8 (Vagifem®) | - | - | - | - | - | - | - | - |
| Vulvovaginal pruritus | 8 (Vagifem®) | - | - | - | - | - | - | - | - |
| Vulvovaginitis | - | 0.9 to 5.3 (vaginal ring) | - | - | - | - | - | - | - |
| **Respiratory** | | | | | | | | | |

| Adverse Event | Estradiol | Estradiol Acetate | Estradiol Cypionate* | Estradiol Valerate* | Estrogens, Conjugated Equine* | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified* | Estrop-ipate† |
|---|---|---|---|---|---|---|---|---|---|
| Asthma | 1.1 to 3.4 (Alora®) | - | - | - | - | - | - | - | - |
| Bronchitis | 3.4 to 7.9 (Alora®)/1.0 to 3.0 (Estring®)/6.0 (Menostar®) | 1.1 to 2.0 (tablet) | - | - | - | - | 0 to 7 | - | - |
| Cough increased | 1.1 to 4.4 (Alora®) | - | - | - | 4 to 7 (tablet) | 6 | - | - | - |
| Nasopharyngitis | 4.1 to 5.7 (Divigel®)/8.5 to 10.3 (Elestrin®)/1.0 to 5.0 (Evamist®)/6.4 to 19.6 (Vivelle-Dot®) | 0 to 1.5 (tablet)/ 1.8 (vaginal ring) | - | - | - | - | - | - | - |
| Pharyngitis | 2.2 to 4.5 (Alora®)/0.5 to 7.0 (Climara®)/1.0 (Estring®) | - | - | - | 10 to 12 (tablet) | 1.9 to 8.0 | - | - | - |
| Pneumonia | 0.6 to 4.5 (Alora®) | - | - | - | - | - | - | - | - |
| Respiratory infection | 16.1 to 24.7 (Alora®) | - | - | - | - | - | - | - | - |
| Rhinitis | 2 to 6 (Climara®) | - | - | - | 6 to 10 (tablet) | 5.7 to 8.0 | 4 to 7 | - | - |
| Sinus congestion | 0 to 6.5 (Vivelle-Dot®) | - | - | - | - | - | - | - | - |
| Sinusitis | 6.7 to 12.2 (Alora®)/4.0 to 5.0 (Climara®)/6.0 (Estrasorb®)/4.0 (Estring®)/5.3 to 13.1 (Vivelle-Dot®) | 1.0 to 1.5 (tablet)/ 1.8 to 3.6 (vaginal ring) | - | - | 6 to 11 (tablet) | - | 3 to 7 | - | - |
| Upper respiratory tract infection | 6.0 to 17.0 (Climara®)/1.6 to 5.7 (Divigel®)/3.5 to 5.9 (Elestrin®)/5.0 (Estring®)/16.0 (Menostar®)/5.0 (Vagifem®)/4.5 to 10.7 (Vivelle-Dot®) | 0 to 3.0 (tablet)/ 3.6 to 4.4 (vaginal ring) | - | - | 9 to 12 (tablet) | 13.2 | - | - | - |
| **Skin** | | | | | | | | | |
| Acne | - | - | - | - | 1.4 (vaginal cream) | - | - | - | - |
| Application site reaction | 5.7 to 56.7 (Alora®)/9.0 (Menostar®) | - | - | - | - | - | - | - | - |
| Chloasma or melasma that may persist when drug is discontinued | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Cyst | 0 to 6.7 (Alora®) | - | - | - | - | - | - | - | - |
| Dermatitis | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Erythema multiforme | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Erythema nodosum | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Hemorrhagic eruption | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Hemorrhoids | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Hirsutism | 0.6 to 4.5 (Alora®) | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Loss of scalp hair | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Pruritus | 1.1 to 6.7 (Alora®)/0.5 to 6.0 (Climara®)/4.0 (Estrasorb®) | - | ✔ | ✔ | ✔ (injection)/ 4.0 to 5.0 (tablet)/ 0.7 to 1.4 (vaginal cream) | - | - | ✔ | - |
| Rash | 2.9 to 8.9 (Alora®) | - | ✔ | ✔ | ✔ (injection) | 4 | - | ✔ | - |

| Adverse Event | Estradiol | Estradiol Acetate | Estradiol Cypionate* | Estradiol Valerate* | Estrogens, Conjugated Equine* | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified* | Estrop-ipate† |
|---|---|---|---|---|---|---|---|---|---|
| Skin hypertrophy | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| **Other** | | | | | | | | | |
| Accidental injury | 4.5 to 8.9 (Alora®)/14.0 (Menostar®) | - | - | - | 6 to 12 (tablet) | - | 3 to 8 | - | - |
| Aggravation of porphyria | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Allergy | 1 (Estring®) | - | - | - | - | - | - | - | - |
| Allergic reaction | 0.6 to 4.5 (Alora®) | - | - | - | - | - | - | - | - |
| Anaphylactoid/ anaphylactic reactions | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Angioedema | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Arthralgia | 1.1 to 12.4 (Alora®)/1.0 to 5.0 (Climara®)/3.0 (Estring®)/1.0 to 4.0 (Evamist®)/12.0 (Menostar®)/3.8 to 8.5 (Vivelle-Dot®) | 1.8 (vaginal ring) | ✔ | ✔ | ✔ (injection)/ 7 to 14 (tablet) | 9.4 to 25.0 | - | ✔ | - |
| Arthritis | 4 (Estring®)/5 (Menostar®) | - | - | - | - | - | - | - | - |
| Back pain | 3.3 to 7.9 (Alora®)/4.0 to 9.0 (Climara®)/6.0 (Estring®)/3.0 to 5.0 (Evamist®)/7.0 (Vagifem®)/7.7 to 10.6 (Vivelle-Dot®) | 0 to 3.0 (tablet)/ 3.6 to 6.2 (vaginal ring) | - | - | 13 to 14 (tablet) | 14 | - | - | - |
| Bone fracture spontaneous | 0 to 3.3 (Alora®) | - | - | - | - | - | - | - | - |
| Changes in libido | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Changes in weight | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Edema | 0.5 to 13.0 (Climara®) | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | ✔ |
| Exacerbation of asthma | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Family stress | 2 (Estring®) | - | - | - | - | - | - | - | - |
| Fever | - | - | - | - | - | 1 | - | - | - |
| Flu syndrome | 3.4 to 13.3 (Alora®)/3.0 (Estring®) | - | - | - | 10 to 11 (tablet) | - | 4 to 7 | - | - |
| Fungal infection | 0 to 10.0 (Alora®) | 1 to 3 (tablet) | - | - | - | - | - | - | - |
| Genital disorder | - | 2.7 (vaginal ring) | - | - | - | - | - | - | - |
| Glucose intolerance | - | - | - | - | ✔ (injection) | - | - | - | - |
| Hot flashes | 2 (Estring®)/0 to 6.4 (Vivelle-Dot®) | - | - | - | - | - | - | - | - |
| Hypocalcemia | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Increased triglycerides | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |
| Increased weight | 0.6 to 4.5 (Alora®)/1.9 to 8.5 (Vivelle-Dot®) | - | - | - | - | 5.7 | - | - | - |
| Infection | 1.1 to 3.4 (Alora®)/12.0 (Estrasorb®)/5.0 (Menostar®) | - | - | - | 18 to 23 (tablet) | 1.9 to 14.0 | - | - | - |
| Influenza | 2.3 to 8.5 (Vivelle-Dot®) | 0 to 2.3 (tablet) | - | - | - | - | - | - | - |
| Injection site edema | - | - | - | - | ✔ (injection) | - | - | - | - |
| Injection site pain | - | - | - | - | ✔ (injection) | - | - | - | - |
| Injection site phlebitis | - | - | - | - | ✔ (injection) | - | - | - | - |
| Joint disorder | 1.1 to 4.5 (Alora®) | - | - | - | - | - | - | - | - |
| Leg cramps | - | - | ✔ | ✔ | ✔ (injection)/ 3 to 7 (tablet) | 10 | - | ✔ | - |
| Leg edema | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |

| Adverse Event | Estradiol | Estradiol Acetate | Estradiol Cypionate* | Estradiol Valerate* | Estrogens, Conjugated Equine* | Estrogens, Conjugated, Synthetic A | Estrogens, Conjugated, Synthetic B | Estrogens, Esterified* | Estrop-ipate† |
|---|---|---|---|---|---|---|---|---|---|
| Metabolic and nutritional disorders | 12 (Menostar®) | - | - | - | - | - | - | - | - |
| Moniliasis | 6 (Estring®)/5 (Vagifem®) | - | - | - | 0.7 to 1.4 (vaginal cream) | - | - | - | - |
| Muscle cramp | - | - | - | - | 1.4 (vaginal cream) | - | - | - | - |
| Myalgia | 1.7 to 5.6 (Alora®)/5.0 (Menostar®) | - | - | - | 5 to 9 (tablet) | 3.8 to 28.0 | - | - | - |
| Neck pain | 3.1 to 6.4 (Vivelle-Dot®) | - | - | - | - | - | - | - | - |
| Otitis media | 0 to 3.4 (Alora®)/1.0 to 3.0 (Estring®) | - | - | - | - | - | - | - | - |
| Pain | 5.6 to 10.1 (Alora®)/1.0 to 11.0 (Climara®)/13.0(Menostar®)/4.3 to 6.2 (Vivelle-Dot®) | - | - | - | 17.0 to 20.0 (tablet)/0.7 to 1.4 (vaginal cream) | 11.3 to 11.0 | 10 to 19 | - | - |
| Pain in limb | 4.3 to 7.7 (Vivelle-Dot®) | 0.9 to 2.7 (vaginal ring) | - | - | - | - | - | - | - |
| Pelvic pain | - | - | - | - | 2.8 to 2.9 (vaginal cream) | - | - | - | - |
| Peripheral edema | 1.7 to 4.4 (Alora®) | - | - | - | - | 10 | - | - | - |
| Reduced carbohydrate tolerance | - | - | ✔ | ✔ | - | - | - | ✔ | ✔ |
| Sinus headache | 1.5 to 10.9 (Vivelle-Dot®) | - | - | - | - | - | - | - | - |
| Skeletal pain | 2 (Estring®) | - | - | - | - | - | - | - | - |
| Tooth disorder | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Toothache | 1 to 3 (Estring®) | - | - | - | - | - | - | - | - |
| Urticaria | - | - | ✔ | ✔ | ✔ (injection) | - | - | ✔ | - |

*Adverse events have been reported with estrogen and/or progestin therapy (estrogens, conjugated equine injection formulation only).
†Adverse events have been reported with estrogen therapy.
-Incidence not reported or <1%
✔ Incidence not specified.

**Table 8. Adverse Drug Events (%) for the Estrogens-Combination Products[25-34]**

| Adverse Event | Estradiol and Drospirenone | Estradiol and Levonorgestrel | Estradiol and Norethindrone | Estradiol and Norgestimate | Estrogen, Conjugated Equine and Medroxyprogesterone | Ethinyl Estradiol and Norethindrone |
|---|---|---|---|---|---|---|
| Abdominal pain | - | 4.2 | 6 to 14* | - | 13 to 23 | 5.3 to 10.2 |
| Accidental injury | - | 3.3 | 3 to 17 | - | 4 to 10 | - |
| Acne | - | - | 4 to 5* | - | - | - |
| Anxiety | - | - | - | - | 2 to 5 | - |
| Application site reaction | - | 40.6 | 2 to 23* | - | - | - |
| Arthralgia | - | 4.2 | 6* | 9 | 7 to 13 | 2.9 to 5.8 |
| Asthenia | - | - | 8 to 13* | - | 6 to 10 | - |

| Adverse Event | Estradiol and Drospirenone | Estradiol and Levonorgestrel | Estradiol and Norethindrone | Estradiol and Norgestimate | Estrogen, Conjugated Equine and Medroxyprogesterone | Ethinyl Estradiol and Norethindrone |
|---|---|---|---|---|---|---|
| Back pain | - | 6.1 | 3 to 15 | 12 | 13 to 16 | 4.7 to 5.3 |
| Breast enlargement | - | - | 2 to 7* | - | 2 to 5 | - |
| Breast pain or discomfort | 3.3 to 17.9 | 18.9 | 17 to 48 | 16 | 12 to 38 | 5.3 to 9.0 |
| Bronchitis | - | 4.2 | 3 to 5* | - | - | - |
| Cervical polyp | 1.2 | - | - | - | - | - |
| Cervix disorder | - | - | - | - | 4 to 5 | - |
| Constipation | - | - | 2 to 5* | - | - | - |
| Cough | - | - | - | 5 | 5 to 8 | - |
| Depression | - | 5.7 | 3 to 9* | 5 | 5 to 11 | 3.7 to 5.8 |
| Diarrhea | 2.2 | - | 4 to 14 | - | 5 to 7 | 3.9 to 5.7 |
| Dizziness | - | - | 6 to 7* | 5 | 3 to 5 | - |
| Dysmenorrhea | - | - | 20 to 31* | 8 | 3 to 13 | - |
| Dyspepsia | - | - | 1 to 8* | - | 5 to 8 | 3.1 to 5.3 |
| Edema | - | 3.8 | - | - | - | 15.7 to 16.9 |
| Emotional lability | 1.2 | - | 0 to 6† | - | - | - |
| Endometrial thickening | - | - | 10† | - | - | - |
| Fatigue | - | - | - | 6 | - | - |
| Female genital tract bleeding | 14 | - | - | - | - | - |
| Flatulence | - | 3.8 | 4 to 7* | 5 | 5 to 9 | - |
| Gastroenteritis | - | - | 0 to 6† | - | - | - |
| Gastrointestinal and abdominal pains | 6.0 to 6.5 | - | - | 12 | - | - |
| Headache | 6 | 5.2 | 11 to 25 | 23 | 28 to 37 | 5.7 to 18.2 |
| Hypertension | - | 3.3 | - | - | - | - |
| Hypertonia | - | - | - | - | 3 to 4 | - |
| Infection | - | 3.3 | 3 to 5* | - | 16 to 21 | - |
| Influenza-like symptoms | - | 4.7 | 5 to 9* | 11 | 8 to 12 | - |
| Insomnia | - | - | 0 to 8 | - | 6 to 7 | - |
| Leg cramps | - | - | - | - | 3 to 7 | - |
| Leukorrhea | - | - | 5 to 10* | - | 3 to 9 | - |
| Menorrhagia | - | - | 2 to 5* | - | - | - |
| Menstrual disorder | - | - | 6 to 19* | - | - | - |
| Migraine | 1 | - | - | - | - | - |
| Moniliasis, genital | - | - | 0 to 6† | - | 4 to 8 | - |
| Myalgia | - | - | - | 5 | 4 to 5 | 7.8 to 8.6 |
| Nasopharyngitis | - | - | 21† | - | - | - |
| Nausea | 3.3 | - | 3 to 12 | 6 | 7 to 11 | 5.3 to 33.0 |

| Adverse Event | Estradiol and Drospirenone | Estradiol and Levonorgestrel | Estradiol and Norethindrone | Estradiol and Norgestimate | Estrogen, Conjugated Equine and Medroxyprogesterone | Ethinyl Estradiol and Norethindrone |
|---|---|---|---|---|---|---|
| Nervousness | - | - | 3 to 6* | - | 2 to 3 | 1.6 to 5.4 |
| Ovarian cyst | - | - | 0 to 7† | - | - | - |
| Pain | - | 5.2 | 4 to 19* | 6 | 11 to 20 | - |
| Pain in extremity | - | - | 5† | - | - | - |
| Papanicolaou smear suspicious | - | - | 4 to 8* | - | - | - |
| Pelvic pain | - | - | - | - | 4 to 5 | - |
| Peripheral edema | 2.2 | - | 6* | - | 3 to 4 | - |
| Pharyngitis | - | - | 4 to 10* | 7 | 8 to 13 | - |
| Post-menopausal bleeding | - | - | 5 to 11† | - | - | - |
| Pruritis | - | - | - | - | 4 to 10 | - |
| Rash | - | 2.4 | 5 to 6* | - | 4 to 6 | - |
| Respiratory disorder | - | - | 7 to 13* | - | - | - |
| Rhinitis | - | - | 7 to 22* | - | 6 to 10 | 12.7 to 15.1 |
| Sinusitis | - | 3.8 | 4 to 15 | 8 | 7 to 10 | 8.1 to 9.4 |
| Tooth disorder | - | - | 4 to 6* | 5 | - | - |
| Upper respiratory tract infection | - | 13.2 | 10 to 18† | 21 | 9 to 11 | - |
| Urinary tract infection | - | 3.3 | - | - | - | 3.7 to 6.2 |
| Uterine fibroid | - | - | 0 to 5† | - | - | - |
| Vaginal bleeding | 9 | 36.8 | - | - | - | - |
| Vaginal hemorrhage | - | - | 3 to 26 | - | 1 to 6 | - |
| Vaginitis | - | 1.9 | 6 to 13* | 7 | 4 to 7 | 5.4 to 4.5 |
| Viral infection | - | - | 0 to 6† | 6 | - | 7.0 to 8.6 |
| Vomiting | - | - | - | - | - | 5.3 to 33.0 |
| Vulvovaginal fungal infections | 5.5 | - | - | - | - | - |
| Weight increase | - | 2.8 | 0 to 9† | - | - | - |

*Transdermal patch only.
†Oral therapy only.
-Incidence not reported or <1.0%
✓ Incidence not specified.

**Table 9. Boxed Warning for the Estrogens**[59]

| WARNING |
|---|
| Estrogen-alone therapy:<br>Endometrial cancer: There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.<br><br>Cardiovascular disorders and probable dementia:<br>Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens 0.625 mg alone, relative to placebo.<br><br>The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years or older during 5.2 years of treatment with daily CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.<br><br>In the absence of comparable data, these risks should be assumed to be similar for other doses of conjugated estrogens and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.<br><br>Estrogen plus progestin therapy:<br>Cardiovascular disorders and probable dementia: Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogen 0.625 mg combined with medroxyprogesterone 2.5 mg, relative to placebo. The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years or older during 4 years of treatment with daily conjugated estrogen 0.625 mg combined with medroxyprogesterone 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.<br><br>Breast cancer: The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. In the absence of comparable data, these risks should be assumed to be similar for other doses of conjugated estrogen and medroxyprogesterone, and other combinations and dosage forms of estrogens and progestins. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman. |

## VII. Dosing and Administration

The usual dosing regimens for the estrogens are listed in Table 10.

**Table 10. Usual Dosing Regimens for the Estrogens**[2-34]

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Estradiol | Palliative treatment of advanced androgen-dependent carcinoma of the prostate:<br>Tablet (Estrace®): 1 to 2 mg TID<br><br>Palliative treatment of breast cancer in appropriately selected women and men with metastatic breast cancer: | Safety and efficacy in children have not been established. | Tablet (Estrace®):<br>0.5 mg<br>1 mg<br>2 mg |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | Tablet (Estrace®): 10 mg TID for ≥3 months<br><br><u>Prevention of postmenopausal osteoporosis:</u><br>Tablet (Estrace®): initial, 0.5 mg/day; maintenance, adjust dose as necessary<br><br>Transdermal patch (Alora®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary<br><br>Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary<br><br>Transdermal patch (Menostar®): 14 µg/day applied once weekly<br><br>Transdermal patch (Vivelle-Dot®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary<br><br><u>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:</u><br>Tablet (Estrace®): initial, 1 to 2 mg/day; maintenance, adjust dose as necessary<br><br>Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary<br><br>Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary<br><br>Transdermal patch (Vivelle-Dot®): initial, 0.025 mg/day applied twice weekly; maintenance, adjust dose as necessary<br><br><u>Treatment of moderate to severe vasomotor symptoms associated with menopause:</u><br>Tablet (Estrace®): initial, 1 to 2 mg/day administered cyclically (three weeks on and one week off); maintenance, adjust dose as necessary<br><br>Topical emulsion (Estrasorb®): 3.48 g/day (two pouches)<br><br>Transdermal gel (Divigel®): initial, 0.25 g/day; maintenance, adjust dose as necessary<br><br>Transdermal gel (Elestrin®): initial, 0.87 g/day (one pump); maintenance, adjust dose as necessary<br><br>Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as | | Topical emulsion (Estrasorb®):<br>2.5 mg/g (4.35 mg/1.74 g)<br><br>Transdermal gel (Divigel®):<br>0.25 mg (0.1%)<br>0.5 mg (0.1%)<br>1 mg (0.1%)<br><br>Transdermal gel (Elestrin®):<br>0.87 g/actuation (0.06%)<br><br>Transdermal patch (Alora®):<br>0.025 mg/day<br>0.05 mg/day<br>0.075 mg/day<br>0.1 mg/day<br><br>Transdermal patch (Climara®):<br>0.025 mg/day<br>0.0375 mg/day<br>0.05 mg/day<br>0.06 mg/day<br>0.075 mg/day<br>0.1 mg/day<br><br>Transdermal patch (Menostar®):<br>14 µg/day<br><br>Transdermal patch (Vivelle-Dot®):<br>0.025 mg/day<br>0.0375 mg/day<br>0.05 mg/day<br>0.075 mg/day<br>0.1 mg/day<br><br>Transdermal spray (Evamist®):<br>1.53 mg/spray (1.7%)<br><br>Vaginal cream (Estrace®): |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | necessary<br><br>Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary<br><br>Transdermal patch (Vivelle-Dot®): initial, 0.0375 mg/day applied twice weekly; maintenance, adjust dose as necessary<br><br>Transdermal spray (Evamist®): initial, one spray daily; maintenance, adjust dose as necessary<br><br><u>Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause:</u><br>Tablet (Estrace®): initial, 1 to 2 mg/day administered cyclically (three weeks on and one week off); maintenance, adjust dose as necessary<br><br>Transdermal patch (Alora®): initial, 0.05 mg/day applied twice weekly; maintenance, adjust dose as necessary<br><br>Transdermal patch (Climara®): initial, 0.025 mg/day applied once weekly; maintenance, adjust dose as necessary<br><br>Transdermal patch (Vivelle-Dot®): initial, 0.0375 mg/day applied twice weekly; maintenance, adjust dose as necessary<br><br><u>Treatment of atrophic vaginitis due to menopause:</u><br>Vaginal tablet (Vagifem®): one tablet administered intravaginally for two weeks, followed by one tablet intravaginally twice weekly; in general start treatment with 10 µg<br><br><u>Treatment of moderate to severe urogenital symptoms due to postmenopausal atrophy of the vagina and/or the lower urinary tract:</u><br>Vaginal ring (Estring®): 2 mg vaginal ring inserted as deeply as possible into the upper one-third of the vaginal vault; the ring is to remain in place continuously for three months<br><br><u>Treatment of vulvar and vaginal atrophy:</u><br>Vaginal cream (Estrace®): 2 to 4 g/day administered intravaginally for one to two weeks, followed by ½ the initial dose for a similar period; maintenance, 1 g administered intravaginally one to three times per week (may be used after restoration of the vaginal mucosa has been achieved) | | 0.1 mg/g (0.01%)<br><br>Vaginal ring (Estring®): 2 mg (7.5 µg/day)<br><br>Vaginal tablet (Vagifem®): 10 µg |
| Estradiol acetate | <u>Treatment of moderate to severe vasomotor symptoms associated with menopause:</u><br>Tablet: initial, 0.45 mg/day; maintenance, 0.45 to 1.8 | Safety and efficacy in children have | Tablet (Femtrace®): 0.45 mg |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | mg/day<br><br>Vaginal ring: initial, 0.05 mg/day; maintenance, 0.05 to 0.1 mg/day<br><br>Treatment of moderate to severe vulvar and vaginal atrophy associated with menopause:<br>Vaginal ring: initial, 0.05 mg/day; maintenance, 0.05 to 0.1 mg/day | not been established. | 0.9 mg<br><br>Vaginal ring (Femring®):<br>0.05 mg/day<br>0.1 mg/day |
| Estradiol cypionate | Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:<br>Injection: 1.5 to 2 mg intramuscularly at monthly intervals<br><br>Treatment of vasomotor symptoms associated with menopause:<br>Injection: 1 to 5 mg intramuscularly every three to four weeks | Safety and efficacy in children have not been established. | Injection (intramuscular):<br>5 mg/mL |
| Estradiol valerate | Palliative treatment of advanced prostate cancer:<br>Injection: 30 mg or more intramuscularly every one to two weeks<br><br>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:<br>Injection: 10 to 20 mg intramuscularly every four weeks<br><br>Treatment of vasomotor symptoms associated with menopause:<br>Injection: 10 to 20 mg intramuscularly every four weeks<br><br>Treatment of vulvar and vaginal atrophy associated with menopause:<br>Injection: 10 to 20 mg intramuscularly every four weeks | Safety and efficacy in children have not been established. | Injection (intramuscular):<br>10 mg/mL<br>20 mg/mL<br>40 mg/mL |
| Estrogens, conjugated equine | Palliative treatment of advanced androgen-dependent carcinoma of the prostate:<br>Tablet: 1.25 to 2.5 mg TID<br><br>Palliative treatment of breast cancer in appropriately selected women and men with metastatic disease:<br>Tablet: 10 mg TID for ≥3 months<br><br>Prevention of postmenopausal osteoporosis:<br>Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual clinical and bone mineral density responses<br><br>Treatment of abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology:<br>Injection: 25 mg intramuscularly or intravenously once; repeat in six to 12 hours if necessary | Safety and efficacy in children have not been established. | Injection (intramuscular and intravenous):<br>25 mg<br><br>Tablet:<br>0.3 mg<br>0.45 mg<br>0.625 mg<br>0.9 mg<br>1.25 mg<br><br>Vaginal cream:<br>0.625 mg/g (30 or 42.5 g) |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | Treatment of atrophic vaginitis and kraurosis vulvae:<br>Vaginal cream: initial, 0.5 g/day intravaginally administered cyclically (three weeks on and one week off); maintenance, 0.5 to 2 g<br><br>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:<br>Tablet: 0.3 or 0.625 mg/day administered cyclically (three weeks on and one week off); maintenance, doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium<br><br>Treatment of moderate to severe vasomotor symptoms associated with menopause:<br>Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual patient response<br><br>Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause:<br>Vaginal cream: 0.5 mg/day intravaginally in a twice-weekly continuous regimen or in a cyclic regimen of 21 days of therapy followed by seven days off of therapy<br><br>Treatment of moderate to severe vaginal dryness symptoms of vulvar and vaginal atrophy associated with menopause:<br>Tablet: initial, 0.3 mg/day; maintenance, subsequent dosage adjustment may be made based upon the individual patient response | | |
| Estrogens, conjugated, synthetic A | Treatment of moderate to severe vaginal dryness symptoms of vulvar and vaginal atrophy associated with menopause:<br>Tablet: 0.3 mg/day<br><br>Treatment of moderate to severe vasomotor symptoms associated with menopause:<br>Tablet: initial, 0.45 mg/day; maintenance, 0.45 to 1.25 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>0.3 mg<br>0.45 mg<br>0.625 mg<br>0.9 mg<br>1.25 mg |
| Estrogens, conjugated, synthetic B | Treatment of moderate to severe vasomotor symptoms associated with menopause:<br>Tablet: 0.3 to 1.25 mg/day<br><br>Treatment of moderate to severe vaginal dryness and pain with intercourse, symptoms of vulvar and vaginal atrophy, associated with menopause:<br>Tablet: 0.3 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>0.3 mg<br>0.45 mg<br>0.625 mg<br>0.9 mg<br>1.25 mg |
| Estrogens, esterified | Palliative treatment of breast cancer in appropriately selected women and men with metastatic disease:<br>Tablet: 10 mg TID for ≥3 months | Safety and efficacy in children have not been | Tablet:<br>0.3 mg<br>0.625 mg<br>1.25 mg |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | Palliative therapy of advanced prostatic carcinoma:<br>Tablet: 1.25 to 2.5 mg TID<br><br>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:<br>Tablet (hypogonadism): 2.5 to 7.5 mg/day, in divided doses for 20 days, followed by a rest period of 10 days' duration<br><br>Tablet (female castration, primary ovarian failure): 1.25 mg/day administered cyclically (three weeks on and one week off)<br><br>Treatment of moderate to severe vasomotor symptoms associated with menopause:<br>Tablet: 1.25 mg/day administered cyclically (three weeks on and one week off)<br><br>Treatment of vulval and vaginal atrophy associated with menopause:<br>Tablet: 0.3 to 1.25 mg or more daily administered cyclically (three weeks on and one week off) | established. | 2.5 mg |
| Estropipate | Prevention of osteoporosis:<br>Tablet: 0.75 mg/day for 25 days of a 31-day cycle per month<br><br>Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:<br>Tablet : 1.5 to 9 mg/day for the first three weeks of a theoretical cycle, followed by a rest period of eight to 10 days<br><br>Treatment of moderate to severe vasomotor symptoms associated with menopause and treatment of vulval and vaginal atrophy:<br>Tablet: 0.75 to 6 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>0.75 mg<br>1.5 mg<br>3 mg |
| **Combination Products** | | | |
| Estradiol and drospirenone | Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause:<br>Tablet: 0.5-0.25 mg or 1-0.5 mg QD<br><br>Treatment of moderate to severe vasomotor symptoms due to menopause:<br>Tablet: 1-0.5 mg QD | Safety and efficacy in children have not been established. | Tablet*:<br>0.5-0.25 mg<br>1.0-0.5 mg |
| Estradiol and levo-norgestrel | Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause:<br>Transdermal patch: 0.045-0.015 mg transdermal patch worn continuously for seven days; maintenance, a new 0.045-0.015 mg transdermal patch should be applied weekly during a 28-day cycle | Safety and efficacy in children have not been established. | Transdermal patch:<br>0.045-0.015 mg/day |
| Estradiol and norethindrone | Prevention of postmenopausal osteoporosis:<br>Tablet: 0.5-0.1 or 1-0.5 mg QD | Safety and efficacy in children have | Tablet‡:<br>0.5-0.1 mg<br>(Activella®) |

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:<br>Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle†<br><br>Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause:<br>Tablet: 1-0.5 mg QD<br><br>Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle†<br><br>Treatment of moderate to severe vasomotor symptoms due to menopause:<br>Tablet: 0.5-0.1 or 1-0.5 mg QD<br><br>Transdermal patch: 0.05-0.014 or 0.05-0.25 mg transdermal patch worn continuously; maintenance, a new 0.05-0.014 or 0.05-0.25 mg transdermal system should be applied twice weekly during a 28-day cycle† | not been established. | 1.0-0.5 mg (Activella®)<br><br>Transdermal patch:<br>0.05-0.14 mg<br>0.05-0.25 mg |
| Estradiol and norgestimate | Prevention of postmenopausal osteoporosis, treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, and treatment of moderate to severe vasomotor symptoms due to menopause:<br>Tablet: one tablet QD | Safety and efficacy in children have not been established. | Tablet§:<br>1 mg (estradiol) and 1-0.09 mg (estradiol/ norgestimate) |
| Estrogen, conjugated equine and medroxy-progesterone | Prevention of postmenopausal osteoporosis, treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, and treatment of moderate to severe vasomotor symptoms due to menopause:<br>Tablet: one tablet QD | Safety and efficacy in children have not been established. | Tablet‖:<br>0.3-1.5 mg (Prempro®)<br>0.45-1.5 mg (Prempro®)<br>0.625-2.5 mg (Prempro®)<br>0.625-5 mg (Prempro®)<br>0.625 mg (estrogen, conjugated equine) and 0.625-5 mg (estrogen, conjugated equine/ medroxy-progesterone) (Premphase®) |
| Ethinyl estradiol and norethindrone | Prevention of postmenopausal osteoporosis and treatment of moderate to severe vasomotor symptoms due to menopause:<br>Tablet: one tablet QD | Safety and efficacy in children have not been established. | Tablet#:<br>2.5 µg-0.5 mg (Femhrt®)<br>5 µg-1 mg (Femhrt®) |

QD=once daily, TID=three times daily

*Available in three blisters of 28 tablets.
†Can also be administered in combination with an estradiol transdermal patch. With this regimen, estradiol transdermal patch (0.05 mg) is administered for the first 14 days of a 28-day cycle, followed by estradiol/norethindrone 0.05/0.14 or 0.05/0.25 mg transdermal patch for the remaining 14 days of the 28-day cycle.
‡Activella®: available as 28 tablets in a calendar dial pack dispenser.
§Available in cartons of six pouches. Each pouch consists of a blister card containing three 1 mg estradiol tablets followed by three 1.0/0.9 mg estradiol/norgestimate tablets. The pattern of three estradiol tablets and three combination tablets repeats for a total of 30 tablets per blister card. Each blister card contains 15 tablets of each of the two tablets. The three day phases are alternated continuously during treatment.
‖Prempro®: available as one or three blisters of 28 tablets. Premphase®: available as one blister of 28 tablets.
#Femhrt®: available as bottles of 90 tablets or blisters of 28 tablets.

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the estrogens are summarized in Table 11.

**Table 11. Comparative Clinical Trials with the Estrogens**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Comparative Trials of Estrogens** | | | | |
| WHI Steering Committee[42] (2004)<br>WHI<br><br>CEE 0.625 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women, 50 to 79 years of age, with prior hysterectomy | N=10,739<br><br>6.8 years (mean duration of follow-up) | Primary:<br>Rate of CHD (nonfatal MI or CHD death), invasive breast cancer<br><br>Secondary:<br>Stroke, PE, colorectal cancer, hip fracture, and deaths from other causes | Primary:<br>Treatment with CEE did not significantly affect the incidence of CHD or overall mortality. The estimated HR for CHD was 0.91 (95% CI, 0.75 to 1.12), breast cancer was 0.77 (95% CI, 0.59 to 1.01), and death was 1.04 (95% CI, 0.88 to 1.22). There was an estimated 7 fewer cases of breast cancer among the women treated with CEE compared to the women taking placebo, but that did not reach statistical significance.<br><br>Secondary:<br>Treatment with CEE increased the risk of stroke and reduced the risk of hip and other fractures. The estimated HR for breast cancer was 0.77 (95% CI, 0.59 to 1.01), stroke was 1.39 (95% CI, 1.10 to 1.77), PE was 1.34 (95% CI, 0.87 to 2.06), colorectal cancer was 1.08 (95% CI, 0.75 to 1.55), hip fracture was 0.61 (95% CI, 0.41 to 0.91), and global index was 1.01 (95% CI, 0.91 to 1.12). Thus, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10,000 person-years. |
| Stefanick et al.[60] (2006)<br>WHI<br><br>CEE 0.625 mg<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women, 50 to 79 years of age, with prior hysterectomy | N=10,739<br><br>7.1 years (mean duration of follow-up) | Primary:<br>Breast cancer incidence, tumor characteristics, mammogram findings<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with CEE did not increase the risk of breast cancer compared to placebo. The HR for invasive breast cancer was 0.80 (95% CI, 0.62 to 1.04; P=0.09) and 0.82 (95% CI, 0.65 to 1.04; P=0.10) for total breast cancer.<br><br>However, breast cancer that developed in patients who had received CEE was associated with larger tumor size (P=0.03) and higher percentage of positive nodes (P=0.07) compared to placebo.<br><br>The risk of invasive breast cancer was significantly lower in women who had no prior hormone use. The HR was 0.65 (95% CI, 0.46 to 0.92) for women with no prior hormone use and 1.02 (95% CI, 0.70 to 1.50) for women with prior hormone use (P=0.09). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | There were larger numbers of mammograms with abnormalities that required primarily short interval follow-ups in the CEE group compared to placebo (P<0.001).<br><br>Secondary:<br>Not reported |
| Hsia et al.[61]<br>(2006)<br>WHI<br><br>CEE 0.625 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women 50 to 79 years of age at baseline, who had undergone prior hysterectomy | N=10,739<br><br>7.1 years (mean duration of follow-up) | Primary:<br>CHD events (MI or coronary death)<br><br>Secondary:<br>CABG or PCI, angina, hospitalized CHF, acute coronary syndrome | Primary:<br>There were 201 CHD events reported among the women assigned to estrogen treatment compared to 217 events in the placebo group (HR, 0.95; 95% CI, 0.79 to 1.16).<br><br>The HR was 0.61 (95% CI, 0.25 to 1.50) for the 50 to 59 years age group, 0.86 (95% CI, 0.60 to 1.25) for the 60 to 69 years age group, and 1.10 (95% CI, 0.69 to 1.73) for the 70 to 79 years of age group; P=0.35.<br><br>There was no significant trend in risk of primary outcome over time (P=0.14).<br><br>Secondary:<br>Coronary revascularization was less frequent among the 50 to 59 years age group that was assigned to estrogen treatment (HR, 0.55; 95% CI, 0.35 to 0.86). Composite outcomes were less frequent with estrogen treatment in this age group (HR, 0.66; 95% CI, 0.45 to 0.96).<br><br>There were no differences in secondary coronary outcomes between treatment groups in the women 60 to 69 years of age or women 70 to 79 years of age. |
| LaCroix et al.[62]<br>(2011)<br><br>CEE 0.0625 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women 50 to 79 years of age with prior hysterectomy | N=7,645<br><br>10.7 years (mean duration of follow-up) | Primary:<br>CHD, invasive breast cancer<br><br>Secondary:<br>Stroke, PE, colorectal cancer, hip fracture, death | Primary:<br>The post-intervention risk (annualized risk) for CHD among patients receiving CEE was 0.64% compared to 0.67% with patients receiving placebo (HR, 0.97; 95% CI, 0.75 to 1.25) and 0.26 vs 0.34%, respectively, for breast cancer (HR, 0.75; 95% CI, 0.51 to 1.09).<br><br>Over the entire follow-up, lower breast cancer incidence with CEE persisted and was 0.27% compared to 0.35% with placebo (HR, 0.77; 95% CI, 0.62 to 0.92). Health outcomes were more favorable for younger |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | compared to older women for CHD (P=0.05).<br><br>Secondary:<br>The risk of stroke was no longer evaluated during the post-intervention follow-up period and was 0.36 and 0.41% among patients receiving CEE and placebo (HR, 0.89; 95% CI, 0.64 to 1.24).<br><br>The risk of deep vein thrombosis was 0.17 and 0.27%, respectively, among patients receiving CEE and patients receiving placebo (HR, 0.63; 95% CI, 0.41 to 0.98) and the risk of hip fracture did not differ significantly between the two treatments (0.36 vs 0.28%; HR, 1.27; 95% CI, 0.88 to 1.28).<br><br>The post-intervention risk (annualized risk) for total mortality among patients receiving CEE was 1.47% compared to 1.48% with placebo (HR, 1.00; 95% CI, 0.84 to 1.18).<br><br>Health outcomes were more favorable for younger compared to older patients for total MI (P=0.007), colorectal cancer (P=0.04), total mortality (P=0.04), and global index of chronic disease (P=0.009). |
| Espeland et al.[63] (2004)<br>WHIMS<br><br>CEE 0.625 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women, 65 to 79 years of age, with prior hysterectomy | N=2,808<br><br>5.4 years (mean follow-up duration) | Primary:<br>Global cognitive function as measured by 3MSE<br><br>Secondary:<br>Not reported | Primary:<br>The mean 3MSE scores were 0.26 units lower in the estrogen treatment group compared to placebo group (P=0.04).<br><br>In the group of women with lower cognitive function at baseline, there were significant decreases in 3MSE scores in the estrogen group compared with placebo (P<0.01).<br><br>The RR of having a 10-unit decrease in 3MSE scores, or greater than 2 standard deviations below the mean, was estimated to be 1.47 (95% CI, 1.04 to 2.07).<br><br>Secondary:<br>Not reported |
| Chen et al.[64] (2006)<br>Nurses' Health | PRO<br><br>Postmenopausal | N=28,835<br><br>20 years | Primary:<br>Diagnosis of invasive breast | Primary:<br>The risk of invasive breast cancer was significantly elevated with longer durations of use (P<0.001). The RRs for invasive breast cancer with |

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| Study<br><br>Conjugated estrogens, with various doses but mostly 0.625 mg QD<br><br>vs<br><br>placebo | women who had a hysterectomy | (mean duration not specified) | cancer<br><br>Secondary:<br>Not reported | unopposed estrogen use is 0.96 (95% CI, 0.75 to 1.22) with less than 5 years of use, 0.90 (95% CI, 0.73 to 1.12) with 5 to 9.9 years of use, 1.06 (95% CI, 0.87 to 1.30) with 10 to 14.9 years of use, 1.18 (95% CI, 0.95 to 1.48) with 15.0 to 19.9 years of use, and 1.42 (95% CI, 1.13 to 1.77) with ≥20 years of use.<br><br>The risk of estrogen receptor and progesterone receptor positive breast cancer was significantly higher after 15 or more years of unopposed estrogen use (P<0.001).<br><br>Secondary:<br>Not reported |
| Jackson et al.[65] (2006)<br><br>CEE 0.625 mg daily<br><br>vs<br><br>placebo | RCT<br><br>Postmenopausal women 50 to 79 years of age with hysterectomy | N=10,739<br><br>7.1 years | Primary:<br>Hip fractures and all other fractures<br><br>Secondary:<br>Not reported | Primary:<br>CEE reduced the risk of hip (HR, 0.65; 95% CI, 0.45 to 0.94), clinical vertebral (HR, 0.64; 95% CI, 0.44 to 0.93), wrist/lower arm (HR, 0.58; 95% CI, 0.47 to 0.72), and total fracture (HR, 0.71; 95% CI, 0.64 to 0.80). This reduction did not differ among strata according to age, oophorectomy status, past hormone use, race/ethnicity, fall frequency, physical activity, or fracture history.<br><br>Total fracture reduction was lower in women at the lowest predicted fracture risk in both absolute and relative terms (HR, 0.86; 95% CI, 0.68 to 1.08). The HRs of the global index for CEE were relatively balanced. The summary of fracture is as follows: lowest risk: HR, 0.81; 95% CI, 0.62 to 1.05; midrisk: HR, 1.09; 95% CI, 0.92 to 1.30; highest risk: HR, 1.04; 95% CI, 0.88 to 1.23 (P=0.42).<br><br>Secondary:<br>Not reported |
| Schaefers et al.[66] (2009)<br><br>Transdermal 17β-estradiol 0.014 mg/day (Menostar®) | AC, DB, MC<br><br>Osteopenic postmenopausal women | N=500<br><br>2 years | Primary:<br>Percent change from baseline in bone mineral density at the lumbar spine<br><br>Secondary: | Primary:<br>Lumbar spine bone mineral density increased by 2.4% (95% CI, 1.9 to 2.9) with transdermal 17β-estradiol versus 3.0% (95% CI, 2.5 to 3.5) with raloxifene after two years.<br><br>Secondary:<br>Of those patients taking transdermal 17β-estradiol, 77.3% had no bone loss in the lumbar spine compared to 80.5% of those taking raloxifene. |

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| vs<br><br>raloxifene 60 mg/day | | | Proportion of women with no loss of bone mineral density in lumbar spine, change in bone mineral density at hip, biochemical markers of bone turnover, and safety parameters. | Both treatments were well tolerated. Most women (99% in the transdermal 17β-estradiol group and 100% in the raloxifene group) showed no histological evidence of endometrial stimulation after two years. Mean dense area in breast mammograms was 19.8% in the transdermal 17β-estradiol group vs 19.0% in the raloxifene group after two years. |
| Haines et al.[67] (2009)<br><br>Transdermal estradiol patch (0.014 mg/day)<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Symptomatic postmenopausal Asian women 40 to 65 years of age, had undergone natural menopause, and had ≥24 hot flushes | N=165<br><br>12 weeks | Primary:<br>Relative change in the frequency of all hot flushes from baseline to week 12<br><br>Secondary:<br>Relative changes in frequency of all hot flushes from baseline to weeks four and eight and frequency of moderate to severe hot flushes from baseline to weeks four, eight, and 12; absolute changes in vaginal pH; vaginal maturation value; Menopause QOL scores; occurrence of urogenital symptoms; vaginal | Primary:<br>There was a greater relative reduction in the mean weekly number of all hot flushes at week 12 with estradiol transdermal patch (55%) compared to placebo (40%; P<0.01), as well as at weeks four and eight.<br><br>Secondary:<br>The relative change in the number of moderate and severe hot flushes per week at week 12 was greater with estradiol transdermal patch compared to placebo (-58 vs -39%). The reductions of moderate and severe hot flushes and in any hot flushes were significant (P<0.05) at weeks four, eight, and 12.<br><br>Vaginal pH had fallen significantly with estradiol transdermal patch by week four (5.60±0.76 to 5.10±0.72) and then remained stable throughout the trial. There were no significant changes with placebo. Vaginal pH decreased significantly more with estradiol transdermal patch compared to placebo (P<0.001).<br><br>The vaginal maturation value had increased significantly more with estradiol transdermal patch compared to placebo (absolute change at week 12: 17.40±21.85 vs 5.00±17.04; P<0.001).<br><br>Of the patients with an intact uterus (53 and 46), few had vaginal bleeding or spotting. Any bleeding/spotting was reported by three patients receiving estradiol transdermal patch and four patients receiving placebo in cycle 1, by two and two in cycle 2, by five and two in cycle 3. |

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| | | | bleeding profiles; safety | The absolute mean change in the Menopause QOL scores from baseline to week 12 were not difference between the treatments (-1.00±1.25 and -1.00±1.06, respectively; P value not reported). All subscores improved with both treatments; vasomotor and sexual subscores improved more with estradiol transdermal patch compared to placebo, while the physical subscore improved more with placebo.<br><br>There was considerable improvement from baseline in certain urogenital symptoms with both treatments; however, there were no differences between the two treatments for any symptoms assessed.<br><br>Of the 55 patients who experienced an adverse event, 41.3 and 27.5% received estradiol transdermal patch and placebo. Most events were mild to moderate. The most frequent primary system organ classes with adverse events were the same with both treatments: infections and infestations reproductive system and breast disorders. |
| Buster et al.[68] (2008)<br><br>Transdermal estradiol spray<br><br>vs<br><br>placebo | DB, MC, PG, RCT<br><br>Postmenopausal women with at least eight moderate-to-severe hot flushes per day | N=454<br><br>12 weeks | Primary:<br>Mean change from baseline in frequency and severity of moderate-to-severe hot flushes at weeks four and 12<br><br>Secondary:<br>Safety | Primary:<br>All three dosing regimen groups (one, two or three sprays daily) of the estradiol group showed a significant decrease in hot flushes at weeks four and 12 compared with their placebo groups (P<0.010). The mean change in frequency at week 12 was eight fewer flushes per day for women in the estrogen groups and between four and six fewer flushes for women in the placebo groups.<br><br>Women in the three- and two-estrogen spray groups demonstrated significant (P<0.050) reductions in severity score at weeks four and 12; women in the one-spray group showed significant reductions at week five. At week 12, the majority (74 to 85%) of women on estrogen showed at least a 50% hot flush frequency reduction as compared with 46% in the placebo group. The systemic estrogen delivery rates at week 12 were approximately 0.021, 0.029, and 0.040 mg/d for the one-, two-, and three-spray doses, respectively.<br><br>Secondary:<br>Common adverse events were similar to those previously reported with other transdermal products. Treatment-related application site reaction rate |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | was similar to placebo (1.3 compared to 1.8%). |
| **Comparative Trials of Estrogens With Same Delivery Route** | | | | |
| Mizunuma et al.[69] (2010)<br><br>Estradiol 0.5 mg/day<br><br>vs<br><br>estradiol 1 mg/day<br><br>vs<br><br>placebo<br><br>Patients originally randomized to placebo were switched to estradiol 1 mg/day after 52 weeks for ethical reasons.<br><br>Patients with an intact uterus, received estradiol/ levonorgestrel 0.5 mg/40 µg or 1 mg/40 µg daily.<br><br>All patients received daily calcium and vitamin D supplementation. | DB, MC, PC, RCT<br><br>Japanese women 45 to 75 years of age who had experienced natural menopause or undergone bilateral oophorectomy ≥1 year prior to trial enrollment with osteoporosis; patients with an intact uterus had a diagnostically valid negative endometrial biopsy or, for those from whom no tissue was obtained or tissue was insufficient for diagnosis, an endometrial thickness ≤4 mm on transvaginal ultrasound | N=309<br><br>2 years | Primary:<br>Percentage change in lumbar BMD at 52 weeks, serial percentage change in lumbar BMD during 104 weeks<br><br>Secondary:<br>Change in amenorrhea rate; incidence of endometrial hyperplasia at 52 and 104 weeks; percentage change in bone turnover markers; changes in calcium, inorganic phosphate, and creatinine levels; fractures | Primary:<br>A total of 241 patients completed all assessments. Combined data of patients receiving monotherapy and combination therapy revealed that the percentage change in lumbar BMD at 52 weeks was significantly greater with estradiol 1 (P<0.001) and 0.5 mg (P<0.001) compared to placebo. The increase in BMD was nonsignificantly greater with estradiol 1 mg compared to estradiol 0.5 mg (P value not reported). Lumbar BMD did not change with placebo.<br><br>Mean percentage changes in lumbar BMD continued to increase for 104 weeks, reaching 8.0 and 10.2% at 104 weeks with estradiol 0.5 and 1 mg, respectively. At this point, the difference between estradiol 0.5 and 1 mg was significant (P=0.008). There was a greater percentage change in BMD with estradiol 1 mg compared to estradiol 0.5 mg, both overall and in patients receiving combination therapy. In repeated measurement analysis, neither the estradiol dose nor the presence or absence of levonorgestrel had a significant effect (P=0.058 and P=0.192, respectively).<br><br>The osteoporosis cure rate (percentage of patients with BMD >-2.5 SD of young adult mean) was greater with estradiol 1 mg (44, 50, and 60% of patients at 28, 52, and 104 weeks, respectively) compared to estradiol 0.5 mg (35, 44, and 50%, respectively).<br><br>Secondary:<br>The amenorrhea rate was greater with estradiol/levonorgestrel 0.5 mg/40 µg compared to estradiol/levonorgestrel 1 mg/40 µg at both 52 and 104 weeks.<br><br>Levonorgestrel effectively suppressed possible endometrial proliferation due to estradiol administration. Neither endometrial hyperplasia nor cancer was observed at 52 and 104 weeks among patients who received estradiol/levonorgestrel 1 mg/40 µg. There was no clear difference in the incidence rates of atrophic/inactive endometrium between placebo and combination therapy. Endometrial thickness increased slightly over time with combination therapy without clinical significance. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Intact osteocalcin, bone alkaline phosphatase, type 1 collagen cross-linked N-telopeptide, and deoxypyridinoline all decreased with estradiol treatment to within the reference range, and changes were consistent with the change in BMD. Bone resorption markers decreased first, followed by bone formation markers. Urine type 1 collagen cross-linked N-telopeptide, urine deoxypyridinoline, and serum bone alkaline phosphatase achieved the minimum significant change. Changes in bone formation markers were greater with estradiol 1 mg compared to estradiol 0.5 mg at 52 and 104 weeks, but this was not significant. There was no difference between active treatments in changes in bone resorption markers. There was no excessive suppression of bone turnover markers with active treatment.<br><br>Six patients experienced new fractures in the 104 weeks; four patients receiving placebo, one patient receiving estradiol 0.5 mg, and one patient receiving estradiol 1 mg. Levonorgestrel had no effect on the fracture rate. |
| Good et al.[70] (1996)<br><br>Transdermal estradiol patch (Alora®) 50 µg/day<br><br>vs<br><br>transdermal estradiol patch (Alora®) 100 µg/day<br><br>vs<br><br>placebo | DB, DD, PG, RCT<br><br>Postmenopausal women ≥21 years of age if surgically menopausal or ≥45 years of age if naturally menopausal, amenorrheic for ≥6 months, experiencing ≥60 moderate or severe hot flashes weekly | N=273<br><br>12 weeks | Primary:<br>Reduction in the frequency and severity of hot flashes<br><br>Secondary:<br>Changes in serum concentrations of estradiol, estrone, estrone sulfate, and FSH; improvements in vaginal cytology; global impressions; adverse events | Primary:<br>There was a significant reduction in the frequency of moderate-to-severe hot flashes by week three of treatment with the 50 µg/day dose (P<0.02) and by week two of treatment with the 100 µg/day dose (P<0.001) compared with placebo.<br><br>At the end of the study, there was a reduction in frequency of moderate-to-severe hot flashes by 86.6% with the 50 µg/day dose and by 92.5% with the 100 µg/day dose.<br><br>Forty eight percent of the 50 µg/day group and 68% of the 100 µg/day group did not experience any hot flashes by week 12.<br><br>Secondary:<br>The changes in estradiol, estrone, and estrone sulfate were increased in a dose-dependent manner.<br><br>Serum FSH levels were reduced in a dose-dependent manner.<br><br>Both treatment groups showed improvement in vaginal cytology. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Both treatment groups reported improvement in vaginal dryness, itching and dyspareunia. Greater improvement was reported with the 100 µg/day group.<br><br>The median assessment scores showed patients and investigators rated active treatment as good or excellent and placebo treatment as fair.<br><br>The number of systemic adverse experiences was similar (71.4% of patients on active treatment and 73.6% of patients on placebo). |
| Bowen et al.[71] (1998)<br><br>Transdermal estradiol patch (Alora®) 0.1 mg/day<br><br>vs<br><br>transdermal estradiol patch (Estraderm®) 0.1 mg/day | OL, RCT, XO<br><br>Postmenopausal women between 35 to 65 years of age | N=24<br><br>30 days (11 days of treatment with first drug, then 7 days of washout interval, then crossover to second drug for 11 days of treatment) | Primary:<br>Serum estradiol concentrations; FI defined as $[C_{max} - C_{min}]/C_{av}$<br><br>Secondary:<br>Monitoring metabolism of estradiol to estrone and estrone sulphate, local skin tolerability defined as application site reactions such as erythema and pruritus | Primary:<br>Peak estradiol levels were similar (127.1 for Alora® vs 128.6 for Estraderm®; P=0.5228). However, Alora® had fewer fluctuations in steady-state levels. Alora® had an FI of 0.970±0.226, while Estraderm® had an FI of 1.684±0.452 (P=0.0001).<br><br>Secondary:<br>The peak estrone levels (47.7 vs 36.4) and estrone sulphate levels (1,383.7 vs 1,085.9) were higher with Alora® than Estraderm®.<br><br>There were fewer fluctuations in steady-state levels of estrone (FI of 0.955±0.338 vs 1.351±0.467) and estrone sulphate (FI of 1.031±0.386 vs 1.483±0.366) with Alora® than Estraderm®.<br><br>The incidences of erythema (45.8 vs 25%) and pruritus (45.8 vs 29%) were higher in the Estraderm® group than in the Alora® group.<br><br>There were no severe adverse events reported for either treatment. |
| Ibarra de Palacios et al.[72] (2002)<br><br>Transdermal estradiol patch (Estradot®*) 50 µg/day<br><br>vs | OL, RCT<br><br>Healthy postmenopausal women | N=100<br><br>7 days | Primary:<br>Skin irritation and adhesion, estradiol delivery<br><br>Secondary:<br>Not reported | Primary:<br>The Estradot® group had lower erythema scores and lower incidences of very slight erythema (P=0.0028) than the Climara® group.<br><br>There was more adherence and fewer incidences of detachment with the Estradot® than with Climara® (not statistically significant).<br><br>Both transdermal patches had similar delivery of estradiol.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| transdermal estradiol patch (Climara®) 50 µg/day | | | | Not reported |
| Archer et al.[73] (1994)<br><br>CEE 0.625 mg QD plus MPA 2.5 mg (Group A) or 5 mg (Group B) QD<br><br>vs<br><br>CEE 0.625 mg QD plus MPA 5 mg (Group C) or 10 mg (Group D) QD on the last 14 days of each 28 day cycle<br><br>vs<br><br>placebo QD (Group E) | DB, MC, RCT<br><br>Postmenopausal women | N=1,724<br><br>1 year | Primary:<br>Bleeding patterns<br><br>Secondary:<br>Not reported | Primary:<br>Amenorrhea occurred in 40% of the patients in Group A, 50% of the patients in Group B, 5% of the patients in Group C or D, and 50% of the patients in Group E.<br><br>Regular withdrawal bleeding or spotting occurred in 81.3% of Group C and 77.0% of Group D. There was no bleeding or spotting in 75.5% of Group E.<br><br>Secondary:<br>Not reported |
| Archer et al.[74] (1999)<br><br>Transdermal estradiol 50 µg/day (Vivelle®)<br><br>vs<br><br>transdermal | DB, MC, RCT<br><br>Postmenopausal women, 40 to 70 years of age, with an intact uterus | N=625<br><br>1 year | Primary:<br>Incidences of endometrial hyperplasia, bleeding and/or spotting, vasomotor events<br><br>Secondary:<br>Not reported | Primary:<br>There were significantly fewer cases of endometrial hyperplasia in the estradiol/norethindrone acetate group than in the estradiol group (P<0.001).<br><br>There was a longer mean duration of irregular bleeding or spotting in the estradiol group compared to the estradiol/norethindrone acetate group.<br><br>There was a higher incidence of no uterine bleeding in the estradiol/norethindrone acetate group than in the estradiol group. |

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| estradiol 50 µg plus norethindrone acetate 140, 250, or 400 µg/day (Combipatch®) | | | | Similar reductions in mean number of hot flashes and intensity of sweating were observed with all treatment groups.<br><br>Secondary:<br>Not reported |
| Harrison et al.[75] (2002)<br><br>Transdermal estradiol patch (generic) 0.1 mg/24 hours once weekly, applied to buttocks<br><br>vs<br><br>transdermal estradiol patch (Climara®) 0.1 mg/24 hours once weekly, applied to buttocks | OL, RCT, XO<br><br>Postmenopausal women, 45 to 70 years of age | N=42<br><br>7 days | Primary:<br>Estradiol, estrone, and estrone sulfate levels, application site irritation, patch adhesion<br><br>Secondary:<br>Not reported | Primary:<br>The $C_{max}$ levels for the two treatments were outside the interval of 0.80 and 1.25, suggesting non-bioequivalence when the patches are applied to the buttocks.<br><br>Treatment with the generic estradiol patch vs Climara® resulted in more application site reactions (19.5 vs 2.4%) and skin irritations (three incidences of moderate erythema with generic patch vs 1 incidence of intense erythema with Climara®; P=0.039). Both patches resulted in a score of 0 or no visible reaction by day 5 of treatment.<br><br>Higher incidences of detachment (3 vs 1) and patch lifting (22 vs 6) were reported with the generic patch vs Climara®. Thus, the OR for detachment or lifting of the patch was 6.95 (P<0.001) for the generic estradiol patch compared to Climara®.<br><br>Secondary:<br>Not reported |
| Pornel et al.[76] (1995)<br><br>Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly<br><br>vs<br><br>transdermal estradiol patch | MC, OL, PG, RCT<br><br>Postmenopausal women with moderate-to-severe vasomotor symptoms, 39 to 64 years of age | N=205<br><br>12 weeks | Primary:<br>Mean number of hot flashes per day, severity of menopausal symptoms, erythema and pruritus at application sites<br><br>Secondary:<br>Not reported | Primary:<br>Both treatments resulted in significant improvement in number of hot flashes per day at week 12 (P=0.005). There was no statistically significant difference in mean number of hot flashes between treatment groups at week 12.<br><br>Both treatments showed improvement in the severity of sweats, sleep disturbances, urogenital symptoms, and depression.<br><br>There were less topical adverse events, such as erythema and pruritus, in the Menorest® group compared with the Estraderm® group, which did not reach statistical significance (P=0.15). |

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| (Estraderm®) 50 µg /24 hours twice weekly | | | | Secondary:<br>Not reported |
| Toole et al.[77] (2002)<br><br>Transdermal estradiol patch (Estradot®*) 50 µg/24 hours<br><br>vs<br><br>transdermal estradiol patch (Menorest®†) 50 µg/24 hours | OL, RCT<br><br>Healthy postmenopausal women, 40 to 70 years of age | N=208<br><br>5 weeks | Primary:<br>Skin irritation as measured by erythema<br><br>Secondary:<br>Skin reaction, patch adherence, adhesive residue and sensitization | Primary:<br>There was significantly less skin irritation with Estradot® than Menorest® (P=0.0001).<br><br>Secondary:<br>There were more skin reactions with Menorest® than Estradot® (2.40 vs 0.48%).<br><br>There was a higher number of patches that detached in the Menorest® group compared to Estradot® group (P=0.0253).<br><br>There was a significantly higher percentage of patients with residue in the Menorest® than Estradot® group (10.10 vs 1.92%; P<0.0001).<br><br>There were no differences between groups in sensitization. |
| Erianne et al.[78] (1997)<br><br>Menorest®† matrix (without drug) twice weekly<br><br>vs<br><br>Estraderm® matrix (without drug) twice weekly | MC, OL<br><br>Normal healthy females over 40 years of age | N=275<br><br>21 days | Primary:<br>Skin irritation, pruritus (by direct questioning), and adhesion<br><br>Secondary:<br>Not reported | Primary:<br>There were fewer incidences of skin irritation with Estraderm® compared with Menorest® (11.9 vs 15.9% on the buttocks and 13.7 vs 18.6% on the abdomen).<br><br>There were fewer incidences of pruritus with Estraderm® compared with Menorest® (92.5 vs 95.9% on the buttocks and 88.7 vs 96.3% on the abdomen).<br><br>There were similar percentages of patches that were fully adhered to the buttocks application sites during treatment for both groups. There were more patches fully adhered to the abdomen application sites with the Menorest® group compared to the Estraderm® group (88.7 vs 75.8%).<br><br>Secondary:<br>Not reported |
| Andersson et al.[79] (2000) | OL, RCT, XO<br><br>Healthy | N=20<br><br>8 weeks | Primary:<br>Bioavailability, pharmacokinetics, | Primary:<br>There were no differences between the groups in AUC, $C_{max}$, $C_{min}$, average concentrations, or fluctuations. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly<br><br>vs<br><br>transdermal estradiol (Climara®) 50 µg/24 hours once weekly | postmenopausal women | | tolerability<br><br>Secondary:<br>Not reported | There were three cases of erythema with Menorest® and 21 cases of skin reactions in 15 subjects treated with Climara®.<br><br>There were eight systemic adverse events in 8 subjects treated with Menorest® and 13 systemic adverse events in 10 subjects treated with Climara®.<br><br>Secondary:<br>Not reported |
| Suckling et al.[80] (2006)<br><br>Intravaginal estrogens (creams, tablets, pessaries, and an estradiol-releasing ring) | MA<br><br>Postmenopausal women with vaginitis or vaginal atrophy | N=4,162<br>(19 trials)<br><br>≥3 months | Primary:<br>Efficacy (improvement in vaginal atrophy measured both objectively and subjectively), safety (assessment of endometrial stimulations, breast pain) and acceptability (measures of withdrawal, adherence, acceptability of treatment to women)<br><br>Secondary:<br>Not reported | Primary:<br>The estradiol ring showed an improvement of pruritus (two RCTs: OR, 2.71; 95% CI, 1.66 to 4.43) when compared to estrogen cream. In the ring versus tablets trials, there were significant improvements in the tablet group for vaginal dryness (two RCTs: OR, 0.40; 95% CI, 0.24 to 0.64), dyspareunia (two RCTs: OR, 0.53; 95% CI, 0.36 to 0.78), and frequency (two RCTs: OR, 0.63; 95% CI, 0.41 to 0.95). Compared to the cream group, the tablet group showed an improvement for vaginal dryness (one RCT: OR, 7.00; 95% CI, 1.64 to 29.85).<br><br>The estradiol ring versus placebo ring showed an improvement for freedom of symptoms of dyspareunia (one RCT: OR, 12.67; 95% CI, 3.23 to 49.67). The estrogen tablets versus placebo showed an improvement for burning and itching symptoms (two RCTs: OR, 0.15; 95% CI, 0.10 to 0.20) and dyspareunia (two RCTs: OR, 0.17; 95% CI, 0.12 to 0.23). An improvement in vaginal dryness was seen in the vaginal tablet group when compared to placebo (three RCTs: OR, 0.08; 95% CI, 0.06 to 0.10).<br><br>There were no significant differences between groups (estradiol ring versus estrogen cream, estradiol ring versus estrogen tablets, estriol tablets versus placebo) for the following outcomes: dysuria, nocturia, urgency, urge incontinence, participant symptom improvement in dryness, urge incontinence, soreness and irritation, loss of sexual desire and vaginitis. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Significant findings for the relief of vaginal atrophy favored the cream, ring, and tablets when compared to placebo.<br><br>One trial showed significant adverse effects (including uterine bleeding, breast pain and perineal pain) of CEE cream compared to estradiol tablets (OR, 0.18; 95% CI, 0.07 to 0.50). Two trials showed endometrial overstimulation with CEE cream compared to the ring (OR, 0.29; 95% CI, 0.11 to 0.78).<br><br>Secondary:<br>Not reported |
| **Comparative Trials of Estrogens With Different Delivery Routes** | | | | |
| Yang et al.[81] (2007)<br><br>Oestrogel® gel (1.25 g daily; 2.5 g daily; 5.0 g daily)<br><br>vs<br><br>control (Estriol [Ovestin®] 2 mg/day)<br><br>All women received calcium carbonate, 500 mg/day of elemental calcium. | PRO<br><br>Postmenopausal women | N=82<br><br>1 year | Primary:<br>BMD evaluated by 1 QCT at baseline (before treatment), then at six-month intervals<br><br>Secondary:<br>Not reported | Primary:<br>At 12-month posttreatment of Oestrogel® versus estriol 2 mg/day, Oestrogel® showed the following BMD changes at the respected doses: 1.25 g/day showed BMD change of 4.82%; P=0.017; 2.5 g/day BMD change of 2.72%; P=0.226; and 5.0 g/day BMD change of 8.69%; P=0.051).<br><br>At 6 months, all Oestrogel® groups showed significant increases in lumbar spine BMD after treatment (P<0.05), except for the Oestrogel® gel 1.25 g/day group (P=0.232).<br><br>Secondary:<br>Not reported |
| Polvani et al.[82] (1991)<br><br>Oral CEE, dose not specified<br><br>vs | MC, RCT<br><br>Postmenopausal women | N=460<br><br>6 months | Primary:<br>Menopausal symptoms, bleeding<br><br>Secondary:<br>Not reported | Primary:<br>There were similar improvements in menopausal symptoms and similar effects on the endometrium with both treatments.<br><br>The quality and duration of bleeding were considered more physiological in the transdermal group than in the oral group. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| transdermal estradiol, dose not specified | | | | The transdermal estradiol group showed better compliance and fewer dropouts.<br><br>Secondary:<br>Not reported |
| Cortellaro et al.[83] (1991)<br><br>Transdermal estradiol 0.05 mg/day<br><br>vs<br><br>CEE 0.625 mg orally QD<br><br>Both groups in combination with MPA 10 mg QD on the last 8 days of each cycle. | OL, RCT<br><br>Postmenopausal women | N=45<br><br>4 months | Primary:<br>Menopausal symptoms, lipid profile, serum estradiol levels<br><br>Secondary:<br>Not reported | Primary:<br>Both treatments provided similar relief in postmenopausal symptoms.<br><br>Both treatments resulted in similar reductions in serum TC and LDL-C. There was a significant decrease in serum TG levels with the transdermal estradiol treatment only.<br><br>There were no differences between treatment groups in plasma calcium and phosphorus levels or clotting factors.<br><br>Only transdermal estradiol resulted in early follicular-phase plasma estradiol levels.<br><br>Secondary:<br>Not reported |
| Pattison et al.[84] (1989)<br><br>Transdermal estradiol patch 50 µg/24 hours<br><br>vs<br><br>ethinyl estradiol 20 µg orally QD | DB, XO<br><br>Postmenopausal women | N=25<br><br>Duration not specified | Primary:<br>Menopausal symptoms, vaginal cytology, gonadotropin levels, urinary calcium levels, menstrual pattern, hepatic proteins<br><br>Secondary:<br>Not reported | Primary:<br>Both treatments improved menopausal symptoms and vaginal cytology.<br><br>Both treatments lowered gonadotrophin levels and urinary calcium loss.<br><br>Transdermal estradiol did not have an effect on hepatic function, while oral ethinyl estradiol had adverse effects on hepatic proteins (sex-hormone-binding globulin, plasma renin substrate, and lipoproteins).<br><br>Secondary:<br>Not reported |
| Hirvonen et al.[85] (1987) | DB, XO<br><br>Postmenopausal | N=36<br><br>Duration not | Primary:<br>Menopausal symptoms, lipid | Primary:<br>There were no differences in relief of menopausal symptoms between treatment groups. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Estradiol plus MPA, dose not specified<br><br>vs<br><br>estradiol plus levonorgestrel, dose not specified<br><br>vs<br><br>estradiol valerate 2 mg daily | women | specified | profile, bleeding episodes<br><br>Secondary:<br>Not reported | Women on the estradiol/MPA treatment significantly improved the atherogenic index, which is the LDL-C:HDL-C. Women on the estradiol/levonorgestrel treatment showed deterioration in the atherogenic index.<br><br>There was more withdrawal bleeding in the estrogen plus progestin group than in the unopposed estrogen group (78 vs 22%).<br><br>Secondary:<br>Not reported |
| Place et al.[86] (1985)<br><br>Oral CEE (Premarin®) 0.625 mg or 1.25 mg QD<br><br>vs<br><br>transdermal 17β-estradiol (Estraderm®) 0.1 mg/day | DB, MC, PG, RCT<br><br>Postmenopausal women whose symptoms were satisfactorily controlled with CEE | N=124<br><br>Duration not specified | Primary:<br>Menopausal symptoms, adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>There were no significant differences between the treatment groups in hot flashes, other postmenopausal symptoms such as sweating, insomnia, headache, vaginal symptoms, urinary urgency, global assessment scores or estrogen-related side effects.<br><br>There were minor topical reactions reported with the transdermal estradiol for about 20% of the study period.<br><br>Secondary:<br>Not reported |
| Al-Azzawi et al.[87] (2003)<br><br>Estradiol acetate vaginal ring (Menoring®‡) that releases 50 µg/day of estradiol plus placebo oral tablet QD | DB, MC, PG, PRO, RCT<br><br>Healthy postmenopausal women, <65 years, with moderate-to-severe vasomotor symptoms (defined as ≥20 hot | N=159<br><br>24 weeks | Primary:<br>Hot flashes, night sweats, urogenital symptoms, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>Both treatments resulted in significant improvement in hot flashes and night sweats at 12 and 24 weeks from baseline.<br><br>Reduction in urogenital symptoms was seen with both treatments.<br><br>Both groups reported similar incidences of adverse events, including local effects.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>oral estradiol 1 mg QD plus placebo vaginal ring | flashes/night sweats per week) | | | Not reported |
| Nachtigall.[88] (1995)<br><br>Estradiol vaginal ring that releases 7.5 µg/24 hours of estradiol<br><br>vs<br><br>conjugated estrogen vaginal cream, 2 g three times a week | MC, OL, PG, RCT<br><br>Postmenopausal women with estrogen-deficiency-derived atrophic vaginitis | N=196<br><br>15 weeks | Primary:<br>Urogenital atrophy/ symptoms, physicians' and patients' assessment of symptoms<br><br>Secondary:<br>Frequency of endometrial over stimulation as determined by progestogen challenge test after treatment period | Primary:<br>The vaginal ring and creams produced similar improvements in vaginal dryness, vaginal burning, dyspareunia, and vaginal pH.<br><br>Physicians' and patients' assessment of both treatments were similar.<br><br>Secondary:<br>More patients treated with the cream demonstrated signs of endometrial proliferation or hyperplasia than with the ring (10 vs 5%).<br><br>There were more episodes of bleeding with the progestogen challenge test in the vaginal cream group than the vaginal ring group. |
| Hilditch et al.[89] (1996)<br><br>Oral CEE (Premarin®) 0.625 mg QD<br><br>vs<br><br>transdermal estradiol-17β (Estraderm®) 50 µg twice weekly | DB, RCT<br><br>Women 2 to 7 years after menopause, with intact uterus and ovaries, not currently on hormone therapy, and on average severely symptomatic | N=74<br><br>112 days (four 28-day cycles) | Primary:<br>QOL, determined using the Menopause-Specific QOL Questionnaire<br><br>Secondary:<br>Not reported | Primary:<br>There were significant improvements in QOL scores, but no differences between treatment groups were observed in scores for vasomotor, physical, psychosocial, or sexual domains (P>0.05).<br><br>There was a significant improvement from baseline to 10 weeks in scores for vasomotor and physical domains (P<0.001), while changes from 10 weeks to 14 weeks were not statistically significant.<br><br>There was significant improvement from baseline to six weeks in scores for psychosocial and sexual domains (P<0.01), while changes from six weeks to the end of study were not statistically significant.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Both groups in combination with oral MPA (Provera®) 10 mg QD for the last 12 days of each cycle | | | | Not reported |
| Blanc et al.[90] (1998)<br><br>Percutaneous 17β-estradiol gel 1.5 mg/day (Group A)<br><br>vs<br><br>transdermal 17β-estradiol patch 50 µg/day (Group B)<br><br>vs<br><br>oral estradiol valerate 2 mg QD (Group C)<br><br>All groups in combination with a progestin, nomegestrol acetate 2.5 mg QD | MC, OL, PRO, RCT<br><br>Postmenopausal women, mean, 54.9±0.6 years of age | N=54<br><br>168 days (six 28-day cycles) | Primary:<br>Rate of amenorrhea<br><br>Secondary:<br>Climacteric symptoms | Primary:<br>The amenorrhea rates after one month of treatment were 67 to 83% for Group A, 25 to 56% for Group B, and 53 to 61% for Group C, which were significantly different between groups for the fourth (P=0.008) and fifth (P=0.003) treatment cycles.<br><br>The overall rate of cycles with no bleeding was 78% for Group A, 48% for Group B, and 60% for Group C (P=0.001).<br><br>Secondary:<br>There were no significant differences between groups in relief of climacteric symptoms by the end of the third cycle. |
| Polatti et al.[91] (2000)<br><br>Oral estradiol valerate 2 mg QD for 21 days plus cyproterone | PRO, RCT<br><br>Postmenopausal women with and without uterine myomas | N=240<br><br>2 years | Primary:<br>Risk of uterine myoma onset or progression<br><br>Secondary:<br>Not reported | Primary:<br>Among the patients without uterine myomas at baseline, 5% of the transdermal estradiol/MPA group developed new onset of myomas while no new cases of uterine myomas were reported in the oral estradiol valerate/cyproterone acetate group (P<0.01).<br><br>Among the patients with uterine myomas at baseline, treatment with |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| acetate 1 mg QD for 21 days of each 28-day cycle<br><br>vs<br><br>transdermal estradiol 50 µg for 21 days plus MPA 10 mg orally QD for 10 days of each 28-day cycle | | | | transdermal estradiol/MPA resulted in a mean increase in myoma volumes of 25.3% compared with initial volume of myoma (P<0.01). On the contrary, treatment with oral estradiol valerate/cyproterone acetate resulted in no significant changes in myoma volumes.<br><br>Secondary:<br>Not reported |
| Jarvinen et al.[92] (2001)<br><br>Transdermal estradiol patch (Evorel®‡) 50 µg/24 hours<br><br>vs<br><br>transdermal estradiol gel (Divigel®) 1.0 mg | OL, RCT, XO<br><br>Healthy postmenopausal women | N=24<br><br>18 days | Primary:<br>Estradiol levels<br><br>Secondary:<br>Not reported | Primary:<br>There were no significant differences in peak estradiol levels ($C_{max}$) or area under the time-concentration curve (AUC) between groups.<br><br>Estradiol levels fluctuated more with the patch. The total coefficient of variability for AUC was 39% for the patch versus 35% for the gel.<br><br>Secondary:<br>Not reported |
| Nelson et al.[93] (2004)<br><br>Oral CEE<br><br>vs<br><br>oral 17β-estradiol<br><br>vs<br><br>transdermal 17β- | MA<br><br>Postmenopausal women with hot flashes | N=32 trials<br><br>Duration varied | Primary:<br>Efficacy as measured by relief of hot flashes, adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>The numbers of hot flashes per week were significantly reduced with all forms of estrogen compared with placebo. Treatment with oral CEE resulted in a mean change in the number of hot flashes per week of -19.1 (95% CI, -33.0 to -5.1). Treatment with oral 17β-estradiol group resulted in a mean change of -16.8 (95% CI, -23.4 to -10.2). Treatment with transdermal 17β-estradiol group resulted in a mean change of -22.4 (95% CI, -35.9 to -10.4). There was no significant difference between the agents in treatment of menopausal hot flashes.<br><br>The estrogen agents showed similar short-term adverse effects. Breast tenderness and atypical vaginal bleeding were the most frequently reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| estradiol | | | | adverse effects.<br><br>Secondary:<br>Not reported |
| Studd et al.[94] (1995)<br><br>Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly plus dydrogesterone 20 mg for 12 days of every 28-day cycle<br><br>vs<br><br>CEE (Premarin®) 0.625 mg orally QD plus dydrogesterone 20 mg for 12 days of every 28-day cycle | DB, DD, MC, PG, RCT<br><br>Postmenopausal women 40 to 65 years of age, with moderate-to-severe vasomotor symptoms (defined as ≥21 hot flashes per week) | N=214<br><br>12 weeks | Primary:<br>Number of hot flashes per day<br><br>Secondary:<br>Other menopausal symptoms, severity of hot flashes, global assessment, and hormone levels | Primary:<br>The number of daily hot flashes decreased significantly in both treatment groups compared with baseline (7.14 to 0.92 in the Menorest® group and 6.66 to 0.54 in the Premarin® group). No statistically significant difference was observed between the two treatment groups at 12 weeks (P=0.36).<br><br>Secondary:<br>Menopausal symptoms significantly improved in both treatment groups, with 98% of the patients reporting no severe vasomotor symptoms at 12 weeks. There was no statistically significant difference in menopausal symptoms improvements between the groups.<br><br>There was no statistically significant difference in global assessment scores between groups as reported by the investigator (P=0.63) or the patient (P=0.71).<br><br>There was no significant difference between the groups in mean plasma estradiol (P=0.37) or estrone (P=0.56) levels at posttreatment. The mean estradiol to estrone ratio was similar in both groups (0.72 for Menorest® and 0.70 for Premarin®).<br><br>The number of severe adverse events was similar in both groups (7% for Menorest® and 9% for Premarin®). |
| Good et al.[95] (1999)<br><br>Transdermal estradiol patch (Alora®) 0.05 mg/day administered twice weekly | DB, DD, PG, RCT<br><br>Highly symptomatic postmenopausal women | N=321<br><br>12 weeks | Primary:<br>Frequency and severity of hot flashes<br><br>Secondary:<br>Not reported | Primary:<br>There were no significant differences in the frequency of hot flashes or the frequency of moderate-to-severe hot flashes between the Alora® 0.05 mg/day and CEE 0.625 mg groups or Alora® 0.1 mg/day and CEE 1.25 mg groups at week 12.<br><br>There were no significant differences in vaginal cytology, breast tenderness, and unexpected vaginal bleeding between the transdermal and oral estrogen groups. However, there was a lower incidence of bleeding in the Alora® 0.05 mg/day group. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>transdermal estradiol patch (Alora®) 0.1 mg/day administered twice weekly<br><br>vs<br><br>CEE 0.625 mg QD<br><br>vs<br><br>CEE 1.25 mg QD | | | | Secondary:<br>Not reported |
| Chetkowski et al.[96] (1986)<br><br>Transdermal estradiol 25, 50, 100, or 200 µg per 24 hours<br><br>vs<br><br>oral conjugated estrogens 0.625 or 1.25 mg QD | Dose-response study<br><br>Postmenopausal women | N=23<br><br>Duration not specified | Primary:<br>Levels of estradiol and estrone, renin substrate, SHBG, TBG, CBG, lipoproteins<br><br>Secondary:<br>Not reported | Primary:<br>Transdermal estradiol increased levels of circulating estradiol and estrone, while oral estrogens increased levels of estrone.<br><br>There were significant increases in circulating levels of renin substrate, SHBG, TBG, and CBG with the oral estrogens, but there was no effect with transdermal estradiol.<br><br>The oral estrogens at higher doses showed significant improvement in the concentrations of LDL-C and HDL-C, while transdermal estradiol did not.<br><br>Secondary:<br>Not reported |
| Manonai et al.[97] (2001)<br><br>Estradiol vaginal tablet 25 µg<br><br>vs | RCT<br><br>Postmenopausal women | N=53<br><br>12 weeks | Primary:<br>Urogenital symptoms, vaginal health index, vaginal cytology, endometrial thickness, estradiol level | Primary:<br>There was improvement from baseline to four weeks of treatment with both groups in urogenital symptoms, vaginal health index, and vaginal cytology.<br><br>There were significant improvements in vaginal dryness and dyspareunia with the conjugated estrogen cream compared to vaginal tablet. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| conjugated estrogen cream 1 g | | | Secondary:<br>Not reported | Secondary:<br>Not reported |
| Slater et al.[98]<br>(2001)<br><br>Oral micronized estradiol 1 mg QD for 16 months<br><br>vs<br><br>transdermal estradiol patch 0.05 mg/day or 0.1 mg/day, changed twice weekly for 9 months<br><br>vs<br><br>placebo for 9 months | RETRO<br><br>Healthy postmenopausal women | N=33<br><br>9 to 16 months | Primary:<br>Serum estrone sulfate levels<br><br>Secondary:<br>Not reported | Primary:<br>There were higher levels of serum estrone sulfate after long-term treatment with oral estradiol than transdermal estradiol. The serum estrone sulfate levels were 38.8 ng/mL at 15 months for oral estradiol, 1.8 ng/mL at nine months for transdermal estradiol 0.05 mg/day, and 3.2 ng/mL at nine months for transdermal estradiol 0.1 mg/day.<br><br>The increase in serum estrone sulfate level was only significant in the oral estradiol group when compared to baseline (P<0.01).<br><br>Secondary:<br>Not reported |
| Pornel[99]<br>(1996)<br><br>Transdermal estradiol patch (Menorest®†) 50 µg/24 hours<br><br>vs<br><br>CEE (Premarin®) 0.625 mg/day (Study 1) or transdermal | DB, PG, RCT (Study 1); OL, PG (Study 2)<br><br>Postmenopausal women | N=214 (Study 1)<br><br>N=205 (Study 2)<br><br>Duration not specified | Primary:<br>Hot flashes and other menopausal symptoms, serum estradiol, lipid profile, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>There were improvements in menopausal symptoms with all treatment groups.<br><br>There were no significant differences in serum estradiol levels or systemic adverse events between treatment groups.<br><br>There were small reductions in cholesterol in both studies.<br><br>Menorest® was better tolerated and had a lower incidence of erythema, and pruritus.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| estradiol patch (Estraderm®) 50 µg/24 hours (Study 2) | | | | |
| Ayton et al.[100] (1996)<br><br>Estradiol vaginal ring (Estring®)<br><br>vs<br><br>CEE vaginal cream (Premarin®), 1 g (0.625 mg of CEE) | MC, OL, PG, RCT<br><br>Postmenopausal women with symptoms and signs of urogenital atrophy | N=194<br><br>12 weeks | Primary:<br>Urogenital symptoms<br><br>Secondary:<br>Patient preference | Primary:<br>No significant difference was noted between treatment groups in improvement of vaginal dryness and dyspareunia, resolution of atrophic signs, vaginal mucosal maturation indices, and vaginal pH.<br><br>No significant difference was noted between treatment groups in incidences of intercurrent bleeding episodes.<br><br>Secondary:<br>The vaginal ring was significantly preferred and accepted by more patients than the vaginal cream (P<0.0001). |
| Studd et al.[101] (1996)<br><br>Transdermal estradiol patch (Menorest®†) 50 µg/24 hours twice weekly<br><br>vs<br><br>CEE (Premarin®) 0.625 mg orally QD<br><br>Both groups in combination with dydrogesterone 20 mg orally for the last 12 days of each 28 day cycle | RCT<br><br>Postmenopausal women | N=32<br><br>1 year | Primary:<br>Menopausal symptoms, bone loss prevention as measured by bone mineral density<br><br>Secondary:<br>Not reported | Primary:<br>Both treatments resulted in similar relief of menopausal symptoms (vasomotor, psychological, and urogenital symptoms) and reduction of hot flashes.<br><br>Both treatments resulted in similar lumbar spine and hip densitometry results.<br><br>Both treatments resulted in similar incidences of adverse events.<br><br>Secondary:<br>Not reported |
| Gordon et al.[102] | RCT | N=24 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (1995)<br><br>Study 1:<br>Estradiol patch 0.05 or 0.1 mg/day changed once weekly<br><br>vs<br><br>placebo<br><br>Study 2:<br>Estradiol patch 0.05 or 0.1 mg/day changed once weekly<br><br>vs<br><br>CEE 0.625 mg orally QD | Healthy postmenopausal women with hot flashes | 18 days | Frequency and severity of hot flashes, subjects' and investigators' global assessment of treatment<br><br>Secondary:<br>Not reported | There were significant improvements from baseline in frequency and severity of hot flashes and higher global assessment scores with all treatments in both studies.<br><br>In Study 2, there was more improvement that did not reach statistical significance in hot flashes with the estradiol patch 0.1 mg/day than with CEE and less improvement with estradiol patch 0.05 mg/day than with CEE.<br><br>The patches were generally well tolerated.<br><br>Secondary:<br>Not reported |
| Shifren et al.[103] (2008)<br><br>CEE 0.625 mg/day plus micronized progesterone 100 mg/day for 12 weeks<br><br>vs<br><br>transdermal estradiol 0.05 mg/day plus micronized | OL, XO<br><br>Naturally menopausal women | N=27<br><br>24 weeks | Primary:<br>CRP, IL-6, E- and P-selectin, ICAM-1 and vascular cell adhesion molecule-1, serum amyloid A, transferrin, prealbumin, IGF-I, SHBG, TBG, CBG<br><br>Secondary:<br>Not reported | Primary:<br>Nine parameters changed significantly during oral CEE: CRP (192%; P<0.001); E-selectin (-16.3%; P=0.003); P-selectin (-15.3%; P=0.012); ICAM-1 (-5%; P=0.015); transferrin (5.3%; P=0.024); IGF-I (-30.5%; P<0.001); SHBG (113%; P<0.001); TBG (38%; P<0.001); and CBG (20%; P<0.001).<br><br>With transdermal estradiol, only three parameters changed significantly and to a lesser degree: ICAM-1 (-2.1%; P=0.04); IGF-I (-12.5%; P<0.001); and SHBG (2.6%; P=0.042).<br><br>During oral CEE the intrasubject changes in CRP correlated strongly with the changes in serum amyloid A (r=0.805; P<0.001), and were only weakly associated with the changes in SHBG (r=0.248; non-significant), TBG (0.430; P=0.031), and CBG (r=0.072; non-significant). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| progesterone 100 mg/day for 12 weeks | | | | The log-log relationship between CRP and IL-6 observed at baseline showed a parallel shift during oral CEE, suggesting an amplified hepatic response or a greater sensitivity to IL-6 stimulation.<br><br>Secondary:<br>Not reported |
| Vrablik et al.[104] (2008)<br><br>Oral 17β-estradiol for 12 weeks<br><br>vs<br><br>transdermal 17β-estradiol for 12 weeks | OL, XO<br><br>Hysterectomized women | N=41<br><br>24 weeks | Primary:<br>Plasma lipid and lipoprotein levels, AIP<br><br>Secondary:<br>Not reported | Primary:<br>Oral estrogen replacement therapy resulted in a significant increase in HDL-C and apolipoprotein A-I levels, whereas it significantly decreased TC and LDL-C and increased TG concentrations. Transdermal estrogen replacement therapy had no such effect.<br><br>Oral estrogen replacement therapy led to a significant TG enrichment of HDL-C (0.19±0.06 vs 0.27±0.07 mmol/L, P<0.001) and LDL particles (0.23±0.08 vs 0.26±0.10 mmol/L, P<0.001) compared with baseline, whereas transdermal therapy did not have any effect on lipoprotein subclasses composition.<br><br>The difference between the two treatments was statistically significant for HDL-C:TG and LDL-C:TG (0.27±0.07 vs 0.19±0.05 mmol/L, P<0.001 and 0.26±0.10 vs 0.22±0.07 mmol/L, P<0.001, respectively).<br><br>The transdermal but not oral estrogen replacement therapy significantly reduced the AIP compared with baseline (-0.17±0.26 vs -0.23±0.25; P=0.023), making the difference between the therapies statistically significant (-0.23±0.25 vs -0.18±0.22; P=0.017).<br><br>Oral administration of estrogen replacement therapy resulted in TG enrichment of LDL and HDL particles. Transdermal estrogen replacement therapy did not change the composition of the lipoproteins and produced a significant improvement of AIP. Compared with transdermal estrogen replacement therapy, orally administered estrogen replacement therapy changes negatively the composition of plasma lipoproteins.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Gupta et al.[105] (2008)<br><br>Transdermal estradiol patch<br><br>vs<br><br>vaginal estradiol ring | RCT<br><br>Postmenopausal women | N=24<br><br>12 weeks | Primary:<br>Serum estradiol, estrone, estrone sulfate, FSH, luteinizing hormone, and SHBG were measured by immunoassay at baseline and six and 12 weeks<br><br>Secondary:<br>Not reported | Primary:<br>The estradiol patch significantly increased serum estrone and estradiol levels at six and 12 weeks (P<0.01); there was no significant increase in serum estrone and estradiol levels with the estradiol ring.<br><br>Both the patch and the ring significantly reduced vaginal pH at six (P<0.001) and 12 (P<0.001) weeks and significantly reduced the percentage of vaginal parabasal cells at 12 weeks with no significant difference between the two groups.<br><br>Both preparations increased the proportion of superficial cells; the increase was significant only with the estradiol patch (P=0.04).<br><br>Secondary:<br>Not reported |
| **Trials of Combination Estrogen Products** | | | | |
| Hulley et al.[106] (1998)<br><br>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women with established coronary disease, younger than 80 years of age (mean age was 66.7 years), with an intact uterus | N=2,763<br><br>4.1 years (average follow-up duration) | Primary:<br>Occurrence of nonfatal MI or CHD death<br><br>Secondary:<br>Coronary revascularization, unstable angina, CHF, cardiac arrest, stroke or transient ischemic attack, peripheral arterial disease, all-cause mortality, fractures, cancers, thromboembolic events, gallbladder disease | Primary:<br>There were no significant differences between groups in occurrences of MI or CHD death (HR, 0.99; 95% CI, 0.80 to 1.22).<br><br>There were more CHD events in the hormone-treated group compared with placebo in the first year of treatment and fewer events in years four and five. The HR was 1.52 in year one, 1.00 in year two, 0.87 in year three, and 0.67 in years four and five (P=0.009).<br><br>Secondary:<br>There were no significant differences between groups in the rates of fractures (P=0.59 to 0.82), cancers (P=0.33 to 0.60), and total mortality (P=0.56).<br><br>There were more of the following outcomes in the hormone group compared with the placebo group: venous thromboembolic events (P=0.002), deep vein thromboses (P=0.004), pulmonary emboli (P=0.08), and gallbladder diseases (P=0.05). |
| Hulley et al.[107] (2002) | DB, PC, RCT followed by OL, OS | N=2,321 | Primary:<br>Thromboembolic | Primary:<br>The percentages of patients that reported >80% adherence to hormone |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| HERS and HERSII<br><br>CEE 0.625 mg QD plus MPA 2.5 mg QD<br><br>vs<br><br>placebo | Postmenopausal women with coronary disease and average of 67 years of age at enrollment in study | 4.1 years (HERS) followed by 2.7 years of open-label observational study (HERS II) | events, biliary tract surgery, cancer, fracture, total mortality<br><br>Secondary:<br>Not reported | therapy were 81, 78, 74, 67, 50, and 45% for years one through six, respectively.<br><br>Hormone therapy was associated with a significant increase in the incidence of deep vein thrombosis compared with placebo (4.5 events per 1,000 person-years vs 2.2; P=0.02).<br><br>Hormone therapy was associated with a significant increase in the incidence of PE compared with placebo (2.0 events per 1,000 person-years vs 0.7; P=0.03).<br><br>The incidence of biliary tract surgery was significantly increased with hormone therapy compared with placebo (19.1 events per 1,000 person-years vs 12.9; P=0.005).<br><br>The rate of cancer was 19% higher in the hormone therapy group than in the placebo group, but did not reach statistical significance (P=0.08 to 0.48).<br><br>There were no significant differences in the rates of fractures or death between the groups (P>0.05 for both).<br><br>Secondary:<br>Not reported |
| Grady et al.[43] (2002)<br>HERS and HERSII<br><br>CEE 0.625 mg plus MPA 2.5 mg QD<br><br>vs<br><br>placebo for HERS trial, followed by hormone therapy | DB, MC, PC, RCT<br><br>Postmenopausal women with CHD, average 67 years of age at enrollment | N=2,763<br><br>6.8 years (4.1 years for HERS, then 2.7 years of follow-up for HERS II) | Primary:<br>Nonfatal MI and CHD death<br><br>Secondary:<br>Coronary revascularization, hospitalization for unstable angina or CHF, nonfatal ventricular arrhythmia, sudden death, stroke or | Primary:<br>There were no significant differences in the rates of CHD events between groups. The HR was 0.99 (95% CI, 0.81 to 1.22) in HERS, 1.00 (95% CI, 0.77 to 1.29) in HERS II, and 0.99 (95% CI, 0.84 to 1.17) overall.<br><br>There were no significant differences between groups for nonfatal MI (P>0.05).<br><br>Secondary:<br>There were no significant differences between groups for any of the secondary cardiovascular outcomes (P>0.05 for all) with the exception of higher incidence of nonfatal ventricular arrhythmia in the hormone group compared to the placebo group (HR, 3.30; 95% CI, 1.08 to 10.1). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| prescribed at personal physicians' discretion for HERS II study | | | transient ischemic attack, and peripheral arterial disease | There was no trend of lower risk for CHD events with longer duration of hormone therapy (P=0.18) during the follow-up period of HERS II. |
| Maki et al.[108] (2007)<br><br>CEE 0.625 mg plus MPA 2.5 mg daily QD<br><br>vs<br><br>placebo daily QD<br><br>Treatments were given for 4 months. | DB, MC, PC, RCT<br><br>Generally healthy, postmenopausal women with an intact uterus | N=158<br><br>22 months | Primary:<br>Change from baseline of memory, attention, and subjective cognition<br><br>Secondary:<br>Change from baseline at month four on additional measures of cognitive function, emotional status, sexuality, and sleep | Primary:<br>Except for an increase in sexual thoughts and sexual interest with hormone therapy (P=0.10 and P=0.006, respectively), there were no significant differences on any cognitive or QOL measures.<br><br>Secondary:<br>Compared to placebo, symptomatic women in the hormone therapy group showed an improvement in vasomotor symptoms (P=0.001). Specific data was not provided; however, when compared to baseline and placebo, hormone therapy was associated with an improvement in both the incidence and severity of vasomotor symptoms. |
| Manson et al.[109] (2003)<br>WHI<br><br>CEE 0.625 mg QD plus MPA 2.5 mg, in one tablet, QD<br><br>vs<br><br>placebo | RCT<br><br>Postmenopausal women, 50 to 79 years of age at baseline | N=16,608<br><br>5.2 years (planned duration was 8.5 years) | Primary:<br>CHD (nonfatal MI or death due to CHD)<br><br>Secondary:<br>Not reported | Primary:<br>Hormone therapy was associated with an increase in the risk of CHD. The risk of CHD was highest after the first year of hormone use, with a HR of 1.81 (95% CI, 1.09 to 3.01).<br><br>There was a trend toward a decreasing risk of CHD over time with hormone use, which was statistically significant. The HR for CHD was 1.34 (95% CI, 0.821 to 2.18) after 2 years of hormone therapy, 1.27 (95% CI, 0.64 to 2.50) after 3 years, 1.25 (95% CI, 0.74 to 2.12) after 4 years, 1.45 (95% CI, 0.81 to 2.59) after 5 years, and 0.70 (95% CI, 0.42 to 1.14) after 6 years or longer.<br><br>Secondary:<br>Not reported |
| WHI Writing Group[41] | DB, MC, PC, RCT | N=16,608 | Primary:<br>CHD (nonfatal MI | Primary:<br>The estimated HR for CHD was 1.29 (95% CI, 1.02 to 1.63) and breast |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (2002)<br><br>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, QD<br><br>vs<br><br>placebo | Healthy postmenopausal women, 50 to 79 years of age with an intact uterus | 5.2 years (mean follow-up duration) | and CHD death), invasive breast cancer<br><br>Secondary:<br>Stroke, PE, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes | cancer was 1.26 (95% CI, 1.00 to 1.59).<br><br>Thus, there were absolute excess risk of an additional seven CHD events and eight invasive breast cancers per 10,000 person-years of treatment with CEE plus MPA.<br><br>Secondary:<br>The estimated HR for stroke was 1.41 (95% CI, 1.07 to 1.85), PE was 2.13 (95% CI, 1.39 to 3.25), colorectal cancer was 0.63 (95% CI, 0.43 to 0.92), endometrial cancer was 0.83 (95% CI, 0.47 to 1.47), hip fracture was 0.66 (95% CI, 0.45 to 0.98), and death due to other causes was 0.92 (95% CI, 0.74 to 1.14).<br><br>Thus, there were absolute excess risks of an additional eight strokes and eight PEs per 10,000 person-years of treatment with CEE plus MPA. There were absolute risk reductions of six fewer colorectal cancers and five fewer hip fractures per 10,000 person-years of treatment with hormone therapy. |
| Reeves et al.[110] (2006)<br><br>Estrogen (dose not specified)<br><br>vs<br><br>estrogen plus progesterone (dose not specified)<br><br>vs<br><br>tribolone<br><br>vs<br><br>non estrogen | ES, OS<br><br>Postmenopausal women registered with incident breast | N=14,102 registered with incident breast cancer<br><br>2.7 years (mean time for all women from date of last contact to end of follow-up) | Primary:<br>Incidence of breast cancer and risk of breast cancer<br><br>Secondary:<br>Not reported | Primary:<br>14,102 breast cancers were diagnosed and 11,869 (86%) were invasive.<br><br>The RRs of invasive breast cancer in current users compared with never users of hormone therapy varied according to tumor histology overall (P<0.0001), for users of estrogen-only therapy (P=0.0001), and for users of estrogen-progesterone therapy (P<0.0001).<br><br>RRs for both estrogen-only and estrogen- progesterone therapy were greatest for invasive lobular, mixed ductal-lobular and lobular cancer. These risks were generally higher in current users of combined hormone therapy compared with estrogen-only therapy.<br><br>At estimated duration of use of <5 years, five to nine years, and >10 years, estrogen-only therapy was associated with a lower RR of invasive ductal, lobular, and tubular breast cancer when compared to estrogen plus progesterone therapy.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| therapy | | | | Not reported |
| Rossouw et al.[111] (2007)<br><br>CEE 0.625 mg/day or placebo (women post hysterectomy)<br><br>OR<br><br>CEE 0.625 mg/day plus MPA 2.5 mg/day or placebo (women without hysterectomy) | DB, MC, PC, RCT<br><br>Healthy postmenopausal women, 50 to -79 years of age based on hysterectomy status | N=27,347<br><br>5.2 years (mean follow-up duration | Primary:<br>CHD (nonfatal MI, CHD death, or silent MI) and stroke, mortality and a global index for trial monitoring<br><br>Secondary:<br>Not reported | Primary:<br>In women with less than 10 years since the start of menopause, the HR for CHD was 0.76 (95% CI, 0.50 to 1.16); with 10 to 19 years, 1.10 (95% CI, 0.84 to 1.45); and 20 or more years, 1.28 (95% CI, 1.03 to 1.58) (P=0.02). In women of 50 to 59 years of age, the HR for CHD was 0.93 (95% CI, 0.65 to 1.33). Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12 to 1.56), but risk did not vary significantly by age or time since menopause.<br><br>The effects of hormone therapy on total mortality favored younger women (HR of 0.70 for 50 to 59 years; 1.05 for 60 to 69 years, and 1.14 for 70 to 79 years; P=0.06).<br><br>Secondary:<br>Not reported |
| Saltpeter et al.[112] (2006)<br><br>CEE, oral esterified estrogens or transdermal estrogen, alone or in combination with a progestin<br><br>vs<br><br>placebo, calcium supplementation, or no treatment | MA<br><br>Postmenopausal women | N=33,315 (107 trials)<br><br>1.5 years (mean trial duration; range 0.15 to 5 years) | Primary:<br>Net treatment effects for each analysis were pooled using random effects model, subgroup analysis evaluated the effects of transdermal and oral treatment and treatment in diabetic and nondiabetic women<br><br>Secondary:<br>Not reported | Primary:<br>Subgroup analyses showed that oral agents produced greater reductions in LDL-C:HDL-C (-17.4%; 95% CI, -20.0 to -14.9) than transdermal agents (-8.4%; 95% CI, -13.8 to -2.8; P=0.004). Conjugated estrogens produced greater reductions (-22.4%; 95% CI, -25.6 to -19.1) than oral esterified estrogens (-11.3%; 95% CI, -13.2 to -9.4; P<0.0001). Unopposed estrogens and combined hormone therapy produced similar results.<br><br>Only conjugated estrogens reduced BP (-2.2%; 95% CI, -4.1 to -0.3). Transdermal agents (-0.8%; 95% CI, -3.3 to -1.6) and oral esterified estrogens (-1.3%; 95% CI, -3.1 to -0.5) were not significant.<br><br>In women without diabetes, hormone therapy reduced abdominal fat ( - 6.8%; 95% CI, -11.8 to -1.9), HOMA-IR (-12.9%; 95% CI, -17.1 to -8.6) and new-onset diabetes (RR, 0.7; 95% CI, 0.6 to 0.9). Subgroup analyses showed no significant difference in calculated insulin resistance (HOMA-IR) between transdermal agents and oral agents, conjugated and esterified estrogens, or unopposed and combined treatment.<br><br>In women with diabetes, hormone therapy reduced fasting glucose (-11.5%; 95% CI, -18.0 to -5.1), HOMA-IR (-35.8%; 95% CI, -51.7 to - |

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| | | | | 19.8), LDL-C:HDL-C (-15.7%; 95% CI, -18.0 to -13.5), lipoprotein(a) (-25.0%; 95% CI, -32.9 to -17.1), mean BP (-1.7%; 95% CI, -2.9 to -0.5), E-selectin (-17.3%; 95% CI, -22.4 to -12.1), fibrinogen (-5.5%; 95% CI, -7.8 to -3.2) and plasminogen activator inhibitor-1 (-25.1%; 95% CI, -33.6 to -15.5).<br><br>Secondary:<br>Not reported |
| Chlebowski et al.[113]<br>(2003)<br>WHI<br><br>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women 50 to 79 years of age, with an intact uterus | N=16,608<br><br>5.2 years (mean follow-up duration) | Primary:<br>Breast cancer number and characteristics, frequency of abnormal mammograms<br><br>Secondary:<br>Not reported | Primary:<br>There were more cases of total (HR, 1.24; P<0.001) and invasive (HR, 1.24; P=0.003) breast cancer in the hormone-treated group than in the placebo group.<br><br>Invasive breast cancers in the hormone-treated group compared to placebo group were larger (P=0.04), more likely to be node positive (P=0.03), and diagnosed at a significantly more advanced stage (P=0.04).<br><br>There was a higher percentage of abnormal mammograms in the hormone-treated group than in the placebo group after the first year in all age groups (P<0.001) and in women 50 to 59 years of age (P<0.001) as well.<br><br>Secondary:<br>Not reported |
| Hays et al.[114]<br>(2003)<br>WHI<br><br>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women 50 to 79 years of age, with an intact uterus | N=16,608 (at baseline and at one year)<br>N=1,511 (for subgroup analysis at three years)<br><br>3 years | Primary:<br>QOL measures that included functional status, depression score, sleep quality, sexual functioning, cognitive functioning, and menopausal symptoms<br><br>Secondary:<br>Not reported | Primary:<br>There were significant improvement with hormone therapy compared to placebo from baseline to year one in sleep quality (P<0.001), physical functioning (P<0.001), and bodily pain (P<0.001).<br><br>Among the 574 women 50 to 54 years of age with moderate-to-severe vasomotor symptoms at baseline, hormone therapy at year 1 was associated with significant improvement in sleep (P=0.02) only. All other changes in QOL scores from baseline to year one were nonsignificant (P>0.05 for all).<br><br>There were no clinically significant effects on health-related QOL measures at three years of treatment with hormone therapy (P>0.05 for all measures). |

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| | | | | Secondary:<br>Not reported |
| Shumaker et al.[115] (2003)<br><br>CEE 0.625 mg plus MPA 2.5 mg<br><br>vs<br><br>placebo | RCT<br><br>Women 65 years of age or older, with an intact uterus, free of probable dementia | N=4,532<br><br>5 years | Primary:<br>Incidence of probable dementia<br><br>Secondary:<br>Incidence of mild cognitive impairment | Primary:<br>The rate of probable dementia in the estrogen plus progestin group was significantly higher than in the placebo group (HR, 2.05; 95% CI, 1.21 to 3.48; 45 vs 22 per 10,000 person-years; P=0.01).<br><br>Secondary:<br>There was no significant difference in the rate of mild cognitive impairment between the treatment and placebo groups (HR, 1.07; 95% CI, 0.74 to 1.55; 63 vs 59; P=0.72). |
| Cravioto et al.[116] (2011)<br><br>CEE/MPA 0.625/5.0 mg daily for the first 10 days of every month<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Women with systemic lupus erythematosus with any 2 of the following criteria: amenorrhea ≥6 months, serum FSH ≥30 IU/L, menopausal symptoms, and ≥48 years of age | N=106<br><br>24 months | Primary:<br>Severity of menopausal symptoms<br><br>Secondary:<br>Treatment discontinuation rates and reasons, safety | Primary:<br>Vasomotor factor decreased significantly over time (P=0.002) with differential patterns in relation to treatment (P=0.027); with combination hormone therapy, the reduction was more pronounced compared to placebo, at between 1.5 and 2.0 vs between 0.35 and 0.80 points, respectively (scale of 0 to 6). The score reductions with both treatments were observed since the first month of follow-up. Psychological, subjective-somatic, and organic-somatic factors also showed significant reductions along time (P<0.001), but their patterns were similar with respect to treatment (0.123<P<0.727). With these three factors, baseline scores decreased with both treatments since the first month of follow-up, but a tendency for returning to baseline scores was observed after one year. The sensory-somatic factors did not change significantly over time (P=0.065), nor did the pattern differ between treatments (P=0.968). During the two year follow-up period, global mean scores for all the factors except for subjective-somatic tended to be smaller with combination HT compared to placebo; however, the effect size of this treatment did not reach significance in any of the five factors.<br><br>Secondary:<br>Three patients receiving combination hormone therapy and one patient receiving placebo discontinued the trial due to thrombosis. One patient from each treatment group died due to sepsis. However, neither this medical reason nor the other withdrawal causes were significantly different between the two treatments. |

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| | | | | Few patients reported adverse events during the trial. Headache, nausea, melasma, galactorrhea, and dysmenorrhea were reported with each treatment, intermittently and at low frequency (≤6%). Mastalgia was more common with combination hormone therapy compared to placebo at one and six months of treatment (10.20 vs 13.33%; P<0.03). |
| Van de Weijer et al.[117] (2002)<br><br>17β-estradiol 50, 75, or 100 µg/24 hours for 2 weeks followed by 17β-estradiol/ levonorgestrel (50/10, 75/15, or 100/20 µg/24 hours) for 2 weeks of each month | MC, RCT, XO<br><br>Postmenopausal women | N=468<br><br>1 year | Primary:<br>Bleeding patterns<br><br>Secondary:<br>Not reported | Primary:<br>Higher frequencies of cyclic bleeds, intermittent bleeding, and mean duration of cyclic bleeding were reported with higher dosages of estradiol/levonorgestrel.<br><br>Recurrence of cyclic bleeds was acceptable for 90% of the subjects.<br><br>Secondary:<br>Not reported |
| Sanada et al.[118] (2004)<br><br>CEE 0.625 mg QD plus MPA 2.5 mg QD<br><br>vs<br><br>transdermal estradiol plus MPA 2.5 mg QD | RCT<br><br>Postmenopausal Japanese women who developed serum TG concentrations >150 mg/dL after taking CEE plus MA for 12 months | N=36<br><br>3 months | Primary:<br>TG, VLDL-C, LDL-C, HDL-C<br><br>Secondary:<br>Not reported | Primary:<br>There was a significant decrease in TG and VLDL levels compared with baseline (226.0±43.9 to 110.5±44.1 mg/dL; P<0.01) in the transdermal estradiol group.<br><br>There were no significant changes in the LDL-C and HDL-C levels in the transdermal estradiol group compared with CEE group.<br><br>Secondary:<br>Not reported |
| Cunha et al.[119] (2010)<br><br>Group 1: Placebo | DB, PC, PRO, RCT<br><br>Postmenopausal women receiving estrogen/ | N=60<br><br>6 months | Primary:<br>Climacteric symptoms evaluated by the Blatt-Kupperman | Primary:<br>For both the Blatt-Kupperman Menopause Index and hot flush score, a statistically significant increase in the values were observed at the first evaluation after withdrawing the combination hormone therapy (i.e., after two, four, and six months for Groups 1, 2, and 3), respectively. The hot |

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| vs<br><br>Group 2: estradiol/ norethindrone 1/0.5 mg/day for 2 months, followed by placebo<br><br>vs<br><br>Group 3: estradiol/ norethindrone 1/0.5 mg/day for 4 months, followed by placebo | progestogen hormone therapy in full doses (CEE/MPA, or progesterone equivalents) for ≥6 months, wanting to discontinue combination hormone therapy due to personal reasons, and combination hormone therapy was prescribed to treat climacteric vasomotor symptoms | | Menopause Index and hot flush score at two, four, and six months<br><br>Secondary:<br>Not reported | flush score was statistically different between groups that had already discontinued combination hormone therapy compared to patients who were still receiving treatment at the time of observation; however, there was no significant difference in the first evaluation subsequent to withdrawing combination hormone therapy (two months: Group 1 vs Group 2; P<0.001; Group 1 vs Group 3; P=0.006; and Group 2 vs Group 3; P=0.485; four months: Group 1 vs Group 2; P=1.000; Group 1 vs Group 3; P=0.003; and Group 2 vs Group 3; P=0.010; and six months: Group 1 vs Group 2, Group 1 vs Group 3, and Group 2 vs Group 3; P=1.000 for all).<br><br>Secondary:<br>Not reported |
| Simon et al.[120] (2003)<br><br>Ethinyl estradiol 5 µg plus norethindrone acetate 1 mg, in one tablet, QD<br><br>vs<br><br>placebo<br><br>vs<br><br>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, QD (OL arm) | DB, MC, PG, RCT<br><br>Healthy postmenopausal women with an intact uterus | N=357<br><br>1 year | Primary:<br>Incidence and duration of vaginal bleeding<br><br>Secondary:<br>Not reported | Primary:<br>There were significantly lower incidences of bleeding in the ethinyl estradiol/norethindrone treatment group compared with CEE/MPA group (P<0.05 at all time points).<br><br>There was no difference in bleeding incidences in the ethinyl estradiol/norethindrone treatment group and placebo group at months four, five, and seven through 12 (P>0.05).<br><br>The duration of bleeding and/or spotting was significantly shorter in the ethinyl estradiol/norethindrone group than in the CEE/MPA group (P≤0.05).<br><br>There was a larger percentage of amenorrhea in the ethinyl estradiol/norethindrone group than in the CEE/MPA group (P<0.05).<br><br>Secondary:<br>Not reported |

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| Simon et al.[121] (2001)<br><br>Ethinyl estradiol 5 µg QD<br><br>vs<br><br>ethinyl estradiol 5 µg plus norethindrone acetate 0.25 mg QD<br><br>vs<br><br>ethinyl estradiol 5 µg plus norethindrone acetate 1 mg QD<br><br>vs<br><br>ethinyl estradiol 10 µg QD<br><br>vs<br><br>ethinyl estradiol 10 µg plus norethindrone acetate 0.5 mg QD<br><br>vs<br><br>ethinyl estradiol 10 µg plus | DB, PC, RCT<br><br>Postmenopausal women | N=945<br><br>1 year | Primary:<br>Incidences of bleeding and/or spotting<br><br>Secondary:<br>Not reported | Primary:<br>There were significantly higher percentages of amenorrhea with ethinyl estradiol/norethindrone acetate treatment than CEE/MPA treatment. At the end of six months, the incidence of amenorrhea was significantly lower with 5 µg ethinyl estradiol plus 1 mg NA (P=0.009) and 10 µg ethinyl estradiol plus 1 mg norethindrone acetate (P=0.006) compared with CEE/MPA.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| norethindrone acetate 1 mg QD<br><br>vs<br><br>CEE 0.625 mg plus MPA 2.5 mg QD | | | | |
| Simon et al.[122] (2003)<br><br>1 mg norethindrone acetate/5 µg ethinyl estradiol (FemHRT®)<br><br>vs<br><br>0.625 mg CEE/2.5 mg or 5 mg MPA (Prempro®) | RETRO<br><br>Women who were new users of six hormone therapy regimens | N=7,120<br><br>9 months | Primary:<br>Treatment continuation rates<br><br>Secondary:<br>Not reported | Primary:<br>The treatment continuation rate was significantly higher among women taking FemHRT® compared to Prempro®.<br><br>Significantly higher rates of treatment continuation were observed in women >55 years of age, those who did not switch hormone therapy during the nine months study period, those who received care in the central and northeast regions of the United States, and those who received treatment from obstetricians/gynecologists versus primary care physicians.<br><br>Secondary:<br>Not reported |
| Archer et al.[123] (1999)<br><br>Transdermal estradiol 50 µg/day (Vivelle®)<br><br>vs<br><br>transdermal estradiol 50 µg plus norethindrone acetate 140, 250, or 400 µg/day (Combipatch®) | DB, MC, RCT<br><br>Postmenopausal women, aged 40 to 70, with an intact uterus | N=625<br><br>1 year | Primary:<br>Incidence of endometrial hyperplasia, bleeding and/or spotting, vasomotor events<br><br>Secondary:<br>Not reported | Primary:<br>There were significantly fewer cases of endometrial hyperplasia in the estradiol/norethindrone acetate treated group than in the estradiol group (P<0.001).<br><br>There was a longer mean duration of irregular bleeding or spotting in the estradiol group compared to the estradiol/norethindrone acetate.<br><br>There was a higher incidence of no uterine bleeding in the estradiol/norethindrone acetate group than in the estradiol group.<br><br>Similar reductions in mean number of hot flashes and intensity of sweating were observed with all treatment groups.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Not reported |
| Johnson et al.[124] (2002)<br><br>CEE 0.625 mg plus MPA 2.5 mg, in one tablet, QD (Prempro®)<br><br>vs<br><br>17β-estradiol 1 mg plus norethindrone acetate 0.5 mg, in one tablet, QD (Activella®) | DB, MC, PRO, RCT<br><br>Healthy postmenopausal women | N=438<br><br>6 months | Primary:<br>Bleeding profiles<br><br>Secondary:<br>Lipid profiles | Primary:<br>Treatment with Activella® resulted in a larger percentage of women with no bleeding and no spotting (P=0.001) compared to treatment with Prempro®.<br><br>Secondary:<br>There was a significant improvement in TG (-8.5 vs 11.7%; P<0.001) and TC (-9.1 vs -6.9%) in the Activella® group compared to Prempro® group. |
| Godsland et al.[125] (1993)<br><br>Oral therapy with CEE 0.625 mg QD plus levonorgestrel 0.075 mg QD for 12 days of each 28 day cycle<br><br>vs<br><br>transdermal therapy with continuous 17β-estradiol plus norethindrone acetate 0.25 mg QD for 14 days of each 28-day cycle | PC, RCT<br><br>Postmenopausal women | N=61<br><br>18 months | Primary:<br>Intravenous glucose tolerance tests, plasma glucose, insulin, and C-peptide concentrations<br><br>Secondary:<br>Not reported | Primary:<br>There were no changes in glucose or insulin concentrations with transdermal therapy.<br><br>Oral hormone therapy lowered glucose tolerance and increased plasma insulin response. There was greater insulin resistance compared with baseline during the combined estrogen/progestin phase than in the estrogen only phase.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>placebo | | | | |
| Whitcroft et al.[126] (1994)<br><br>Oral therapy with CEE 0.625 mg QD plus dl-norgestrel 0.15 mg QD for 12 days of each cycle<br><br>vs<br><br>transdermal therapy with 17β-estradiol 0.05 mg QD plus norethindrone acetate 0.25 mg QD for 14 days of each cycle<br><br>vs<br><br>placebo | PC, RCT<br><br>Healthy postmenopausal women | N=61<br><br>3 years | Primary:<br>Fasting serum lipid and lipoprotein concentrations<br><br>Secondary:<br>Not reported | Primary:<br>Both oral and transdermal hormone therapy significantly reduced serum TC (P<0.001) and LDL-C (P<0.01) from three months of treatment and effects were maintained at three years of treatment.<br><br>Both oral and transdermal hormone therapy significantly reduced serum TG concentrations (P<0.05) from six months of treatment and effects were maintained over three years of treatment only with the transdermal group.<br><br>HDL-C declined in both oral and transdermal treatment groups, as well as placebo group (P<0.05 for all).<br><br>Secondary:<br>Not reported |
| Hirvonen et al.[127] (1987)<br><br>Estradiol plus MPA, dose not specified<br><br>vs<br><br>estradiol plus levonorgestrel, | DB, XO<br><br>Postmenopausal women | N=36<br><br>Duration not specified | Primary:<br>Menopausal symptoms, lipid profile, bleeding episodes<br><br>Secondary:<br>Not reported | Primary:<br>There were no differences in relief of menopausal symptoms between treatment groups.<br><br>Women on the estradiol/MPA treatment significantly improved the atherogenic index, which is the LDL-C:HDL-C. Women on the estradiol/levonorgestrel treatment showed deterioration in the atherogenic index.<br><br>There was more withdrawal bleeding in the estrogen plus progestin groups than in the unopposed estrogen group (78 vs 22%). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| dose not specified<br><br>vs<br><br>estradiol valerate 2 mg daily | | | | Secondary:<br>Not reported |
| White et al.[128] (2006)<br><br>Drospirenone 1, 2, or 3 mg with 17β estradiol 1 mg or QD in the morning<br><br>vs<br><br>17β estradiol 1 mg alone QD each morning<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Postmenopausal women, 45 to 75 years of age, with mean seated clinic SBP 140 to 179 mm Hg and DBP between 90 to 109 mm Hg in the untreated state | N=750<br><br>Study duration not specified; placebo phase was 3 to 4 weeks and treatment phase was 8 weeks | Primary:<br>Mean change from baseline at week eight in clinic and in ambulatory SBP<br><br>Secondary:<br>Changes from baseline in the clinic and 24-hour DBP, assessment of the hourly changes in ambulatory SBP and DBP | Primary:<br>While the mean reduction in clinic BP in the 17β estradiol alone group and 1mg drospirenone plus 17β estradiol group was not statistically significant, the mean reductions in clinic BP in the 3 and 2 mg drospirenone plus 17β estradiol groups were statistically significant. These reductions were, -13.8/ -8.5 and -12.1/-9.2 mm Hg, in the 3 and 2 mg drospirenone plus 17β estradiol groups, respectively, while the reductions for placebo were -8.7/-5.0 mm Hg (SBP reductions; P=0.0004 and 0.0195 for 3 and 2 mg doses; and for DBP reductions; P<0.0001 for both).<br><br>Secondary:<br>Measures of ambulatory BP showed significant reductions from baseline at a mean of 24-hour SBP in both the 2 and 3 mg drospirenone plus 17β estradiol treatment groups compared to placebo. These reductions were, -6.1 and -4.7 mm Hg in the 3 and 2 mg drospirenone plus 17β estradiol groups respectively, compared to a mean SBP change in the placebo group of -1.2 mm Hg. (P values for SBP reductions vs placebo were <0.0001 and 0.009 respectively). There were no differences in ambulatory BP for 1 mg drospirenone plus 17β estradiol and 17β estradiol alone vs placebo. |
| Preston et al.[129] (2005)<br><br>Drospirenone with 17β estradiol QD for 28 days<br><br>vs<br><br>placebo QD for 28 days | DB, MC, PC, RCT<br><br>Postmenopausal women, 44 to 70 years of age, with or without type 2 diabetes mellitus and using an angiotensin-converting enzyme or angiotensin II receptor antagonist | N=230<br><br>28 days | Primary:<br>Number and percentage subjects who developed hyperkalemia (K ≥5.5 mEq/L) and changes from baseline in seated clinic BP<br><br>Secondary:<br>Not reported | Primary:<br>No statistical differences were observed in the overall number and percentage of subjects with hyperkalemia for drospirenone with 17β estradiol versus placebo.<br><br>No subject had symptoms or electrocardiographic changes related to hyperkalemia.<br><br>A reduction in BP was observed at -8.6/-5.8 mm Hg in patients receiving drospirenone with 17β estradiol vs -3.7/-2.9 mm Hg in the placebo group; P<0.01 for both SBP and DBP. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Secondary:<br>Not reported |
| White et al.[130] (2005)<br><br>Drospirenone 3 mg with 1 mg 17β estradiol QD in the morning<br><br>vs<br><br>placebo QD in the morning | DB, MC, PC, RCT<br><br>Postmenopausal women, aged 45 to 80 years, with seated clinic SBP of 140 to 159 mm Hg and/or the DBP was 90 to 99 mm Hg | N=213<br><br>Duration not specified | Primary:<br>Mean change from baseline at week 12 in clinic BP<br><br>Secondary:<br>Changes from baseline in the 24-hour systolic and diastolic BPs and heart rate, as well as other ambulatory monitoring parameters and mean changes from baseline of serum potassium | Primary:<br>Mean reductions in clinic BP in the drospirenone with 17β estradiol group averaged -14.1/-7.9 mm Hg, and the respective reductions for the placebo group were -7.1/-4.3 mm Hg (P<0.001 for both SBP and DBP).<br><br>Secondary:<br>Drospirenone with 17β estradiol significantly lowered pulse pressure compared to the placebo group by -3.5 mm Hg (P=0.007). No significant changes were observed in heart rate. |
| Archer et al.[131] (2005)<br><br>Estradiol 1.0 mg<br><br>vs<br><br>estradiol 1.0 mg plus 0.5, 1.0, 2.0, or 3.0 mg of drospirenone (estradiol plus drospirenone) | DB, MC, PG, RCT<br><br>Postmenopausal women with an intact uterus (42 to 75 years of age) | N=1,142<br><br>1 year | Primary:<br>Endometrial hyperplasia<br><br>Secondary:<br>Bleeding patterns, hot flush frequency and severity, urogenital symptoms, and health-related QOL | Primary:<br>Compared to estradiol alone, the combinations of drospirenone and estradiol were effective in protecting against endometrial hyperplasia. The probability of hyperplasia was 0.060 (95% CI, 0.043 to 0.078) for the estradiol monotherapy group, 0.007 for the 2 mg estradiol plus drospirenone group, and nonsignificant for the remaining drospirenone/estradiol groups.<br><br>Secondary:<br>A greater proportion of women in all estradiol plus drospirenone treatment groups had bleeding in cycles one through three compared to women in the estradiol monotherapy group (P<0.001). Beginning at week two, there was a decrease in hot flushes from baseline at all time points (P≤0.008 in all treatment groups). At cycle 13, a decrease in mean body weight from baseline was observed in the 2 mg estradiol plus drospirenone and 3 mg estradiol plus drospirenone groups (P<0.001 for both), while the decrease was not statistically significant in the 0.5 mg estradiol plus drospirenone |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | and 1 mg estradiol plus drospirenone groups. |
| Schurmann et al.[132] (2004)<br><br>Drospirenone 1, 2 or 3 mg combined with estradiol (1 mg)<br><br>vs<br><br>placebo | MC, PC, RCT<br><br>Healthy post-menopausal Caucasian women, 45 to 66 years of age, who complained of at least five moderate-to-severe hot flushes per day on at least 7 of the 14 days preceding the study | N=225<br><br>16 weeks of treatment; followed with 2 weeks of follow-up | Primary:<br>Change in the frequency and the intensity of hot flushes from baseline<br><br>Secondary:<br>Other menopausal symptoms (sweating periods, sleep problems, depressed mood, nervousness, and urogenital symptoms), vaginal bleeding, and adverse events | Primary:<br>Hot flushes significantly decreased in frequency for all treatment groups (range, 86 to 90%) in comparison to placebo (45%; P≤0.001) and remained suppressed at study end, 16 weeks.<br><br>Secondary:<br>Drospirenone and estradiol treatment decreased the intensity and severity of sweating, sleep problems, depression, nervousness, and urogenital symptoms. The majority of the adverse events were mild or moderate, and similar rates were observed in all groups. Furthermore, no serious adverse events or clinically significant laboratory abnormalities were attributed to the treatment. |
| Lin et al.[133] (2011)<br><br>Estradiol/ drospirenone daily<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Chinese postmenopausal women 45 to 65 years of age with moderate to severe vasomotor symptoms; documentation of ≥24 moderate to severe hot flushes over 7 consecutive days during a 3 week screening period; an intact uterus with | N=249<br><br>16 weeks (2 weeks of follow-up) | Primary:<br>Relative change in number of hot flushes per week, absolute changes in the severity of moderate to severe hot flushes and in the severity of all hot flushes from baseline to weeks three to 16<br><br>Secondary:<br>Changes in other climacteric symptoms from baseline to week | Primary:<br>The number of hot flushes per week decreased progressively with both treatments over the 16 week period, but was consistently lower with combination therapy compared to placebo from week two onward. Over the treatment period weeks three to 16, the number of hot flushes per week was 11.1±15.1 and 22.4±17.3 with combination therapy and placebo, representing absolute decreases of 45.9±29.3 and 27.5±28.1, respectively. These absolute changes corresponded to relative decreases in the number of hot flushes per week of 80.4 and 51.9% with combination therapy and placebo, a significant treatment difference of 28.5% in favor of combination therapy (P<0.0001).<br><br>Combination therapy was associated with numerically greater reductions in the severity of moderate to severe hot flushes over weeks three to 16 compared to placebo. The change in severity of all hot flushes between baseline and treatment (weeks three to 16) was -0.61 and -0.43 with combination therapy and patients receiving placebo (P≤0.05). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | endometrial thickness <5 mm, or a normal endometrial biopsy if endometrial thickness >5 mm; last menstrual bleed ≥1 year before, or bilateral oophorectomy ≥6 weeks before, or last natural menstrual bleed ≥6 months previously, with a serum FSH ≥40 mIU/mL; a negative urinary pregnancy test; and a negative bilateral mammography result | | 16, safety | Secondary:<br>Among patients who experienced moderate to severe sweating at baseline, 4.1 (7/169) and 22.2% (12/45) of patients receiving combination therapy and placebo continued to experience moderate to severe sweating at week 16. A significantly higher proportion of patients were free of sweating symptoms after 16 weeks with combination therapy (48.1 vs 73.4%; P<0.0001).<br><br>Among patients who experienced vaginal dryness at baseline, a significantly greater proportion of patients receiving combination therapy no longer had this symptom compared to placebo (87.7 [93/106] vs 60.0% [21/35]; P<0.001).<br><br>Depressive moods, nervousness and pollakiuria followed a similar trend of greater reductions in frequency after 16 weeks of combination therapy compared to placebo, but these differences did not reach significance. Incidences of depressive mood were reduced from 42.1% at baseline to 4.0% after combination therapy, and from 49.2 to 12.5% with placebo. Corresponding values for nervousness were from 50 to 51% with both treatments to 6.9 and 17.9% with combination therapy and placebo. At baseline, pollakiuria was present in 29 to 32% of patients and of these, 90.2 and 72.2% no longer experienced this symptom with combination therapy and placebo.<br><br>Mild to moderate insomnia was present at baseline in 71.6 and 65.6% of patients randomized to combination therapy and placebo. At week 16, similar proportions of patients (17.9 and 19.6%, respectively) continued to experience insomnia with both treatments. Occurrences of nocturia were similar between the two treatments at baseline (33.3 and 37.7%), and of these patient, 75.9 and 81.0% of patients were free from this symptom at week 16.<br><br>The proportion of patients free from arthralgia increased from 44.3% at baseline to 75.1% after combination therapy, and from 29.5 to 58.9% with placebo. Proportion of patients free from myalgia increased from 69.9 to 86.1% with combination therapy, and from 57.4 to 78.6% with placebo. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Results for the Clinical Global Impressions scale assessment in patients available at week 18 showed a more favorable effect for combination therapy compared to placebo; 87.9 vs 47.3% of patients were 'much improved' or 'very much improved' (P<0.001).<br><br>A higher proportion of patients receiving combination therapy experienced bleeding and spotting compared to placebo (number of bleeding/spotting days in each 28-day period: 1.7 to 4.8 vs 0.2 to 0.9 days). The cumulative amenorrhea rate in patients who completed the trial increased from 34.4% after cycle one to 67.2% after cycle four with combination therapy, and from 85.2 to 93.4% with placebo.<br><br>A total of 71 patients (29.1 vs 26.2%) reported at least one adverse event, including 46 patients reporting a possibly treatment-related event (20.8 vs 13.1%). The most common adverse event was breast tenderness (8.7 vs 1.6%). The majority of events were mild to moderate in severity, with severe events including breast tenderness, headache, breast swelling, ankle fracture, increased blood TGs, joint swelling, and abdominal neoplasm. Three serious adverse events were reported and were considered to be nontreatment-related. |
| Rowan et al.[134] (2006)<br><br>Study 1: Norethindrone acetate/ethinyl estradiol at either 0.2 mg/1 µg, 0.5 mg/2.5 µg, 1 mg/5 µg, or 1 mg/10 µg, or placebo<br><br>Study 2: norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg, 1 mg/5 | Post-hoc analysis of 3 studies<br><br>Study 1=DB, MC, PC, PG; postmenopausal women<br><br>Study 2=DB, MC, PG; postmenopausal women<br><br>Study 3=DB, MC, PC, PG; postmenopausal women | N= 220,531<br><br>Study 1=16 weeks<br><br>Study 2=12 weeks<br><br>Study 3=24 months | Primary: Postmenopausal symptoms, the effects on bone and endometrium<br><br>Secondary: Not reported | Primary:<br>In study 1, norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg was associated with significant reductions from baseline in mean weekly total hot flush frequency from week 4 (63.6%) through week 16 (73.7%; P<0.05).<br><br>In study 2, the frequency of moderate or severe hot flushes was decreased by 61.1% at week 4 (P<0.05) and by 82.2% at week 12 (P<0.001) with norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg. Furthermore, the mean intensity score was significantly lower than that with placebo at weeks eight and 12 (for both; P=0.001).<br><br>In study 3, the cumulative amenorrhea rates were approximately 90% in the norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg and placebo groups at 12 months. At 24 months, lumbar spine bone mineral density was maintained with norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg, but was significantly decreased from baseline at 7.4% in the placebo group |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| µg, or 1 mg/10 µg, or placebo<br><br>Study 3: Progestin/estrogen therapy (norethindrone acetate/ethinyl estradiol 0.2 mg/1 µg, 0.5 mg/2.5 µg, 1 mg/5 µg, or 1 mg/10 µg), unopposed estrogen monotherapy (ethinyl estradiol 1, 2.5, 5, or 10 µg), or placebo | | | | (P<0.001). At 24 months, endometrial hyperplasia was not observed in the group receiving norethindrone acetate/ethinyl estradiol 0.5 mg/2.5 µg.<br><br>Secondary:<br>Not reported |
| Battaglia et al.[135] (2009)<br><br>Estradiol/ drospirenone 1 mg/2mg<br><br>vs<br><br>estradiol/ norethisterone acetate 1 mg/0.5mg | RCT<br><br>Postmenopausal women | N=30<br><br>6 months | Primary:<br>Effects on BP and other surrogate markers of cerebrovascular and cardiovascular risk.<br><br>Secondary:<br>Not reported | Primary:<br>The basal pulsatility index and the back pressure of the ophthalmic artery were similar in groups 1 and 2. After six months, no changes were observed.<br><br>The nitrites/nitrates values were not different between groups 1 and 2 both in basal conditions and after therapy.<br><br>The brachial artery flow-mediated vasodilatation and the pulsatility index of the brachial artery did not show any difference in groups 1 and 2 both in basal conditions and after the therapy.<br><br>The 24-hour BP monitoring showed no significant differences in the 24-hour time, daytime, and nighttime values either in basal conditions or after therapy.<br><br>All participants were found to be dippers normally (nocturnal reduction ≥10% in comparison with diurnal values). The wake-up BP values were similar in the studied participants. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Secondary:<br>Not reported |
| Furness et al.[136] (2009)<br><br>Estrogen therapy, combined continuous estrogen-progestin therapy, sequential estrogen-progestin therapy | MA<br><br>Postmenopausal women 40 to 75 years of age | N = 38,702 (45 RCT)<br><br>>12 months | Primary:<br>Frequency of endometrial hyperplasia (of any type) or adenocarcinoma (assessed by endometrial biopsy)<br><br>Secondary:<br>Adherence to therapy, rates of additional interventions, and withdrawals due to adverse events | Primary:<br>Unopposed estrogen was associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years.<br><br>For women with a uterus, the risk of endometrial hyperplasia with hormone therapy comprising low dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate or 1.5 mg MPA is not significantly different from placebo (1 mg estradiol/norethindrone acetate: OR, 0.04; 95% CI, 0 to 2.8; 1.5 mg MPA: no hyperplasia events).<br><br>Secondary:<br>Adherence was greater in both continuous and sequentially combined regiments than in unopposed estrogen regimens. There were significant numbers of participants in most of the trials included who withdrew from the trial prior to completion (10 to 50%) due to adverse events, lack of efficacy, or other reasons. Only one study assessed the rate of unscheduled biopsies and found a significant increase associated with moderate dose unopposed estrogen therapy (1 RCT: OR, 11.8; 95% CI 7.0 to 19.9). |
| Canonico et al.[137] (2008)<br><br>Oral estrogen with or without progestogen<br><br>vs<br><br>transdermal estrogen with or without progestogen | MA of 8 OS and 9 RCT<br><br>Women using hormone replacement therapy (age not reported) | N=not reported<br><br>Duration varied | Primary:<br>Risk of VTE<br><br>Secondary:<br>Not reported | Primary:<br>MA of OS showed that oral estrogen but not transdermal estrogen increased the risk of VTE. Compared to nonusers of estrogen, the OR of first-time VTE in current users of oral estrogen was 2.5 (95% CI, 1.9 to 3.4) and in current users of transdermal estrogen was 1.2 (0.9 to 1.7). Past users of oral estrogen had a similar risk of VTE to never users (P values were not reported).<br><br>The risk of VTE in women using oral estrogen was higher in the first year of treatment compared to treatment for more than one year (P<0.05).<br><br>No noticeable difference in the risk of VTE was observed between unopposed oral estrogen and opposed oral estrogen.<br><br>Results from nine RCTs confirmed the increased risk of VTE among |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | women using oral estrogen (2.1; 95% CI, 1.4 to 3.1; P value not reported).<br><br>The combination of oral estrogen and thrombogenic mutations or obesity further enhanced the risk of VTE, whereas transdermal estrogen did not seem to confer additional risk in women at high risk of VTE.<br><br>Secondary:<br>Not reported |
| Morch et al.[138] (2009)<br><br>Oral, transdermal, and vaginal estrogen products with or without a progestogen component | PRO cohort study<br><br>Danish women 50 to 79 years of age from 1995 through 2005 who had no hormone-related cancers before study entry | N=909,949<br><br>Average follow-up 8 years | Primary:<br>Incidence of ovarian cancer<br><br>Secondary:<br>Not reported | Primary:<br>Compared to women who never took hormone therapy, current users of hormones had incidence rate ratios for all ovarian cancers of 1.38 (95% CI, 1.26 to 1.51) and 1.44 (95% CI, 1.30 to 1.58) for epithelial ovarian cancer (P values not reported).<br><br>The risk declined with years since last use: 0 to 2 years, 1.22; >2 to 4 years, 0.98; >4 to 6 years, 0.72, and >6 year, 0.63.<br><br>For current users the risk of ovarian cancer did not differ significantly with different hormone therapies or duration of use.<br><br>The incidence rates in current and never users of hormones were 0.52 and 0.40 per 1,000 years, respectively, for an absolute risk increase of 0.12 (95% CI, 0.01 to 0.17 per 1,000 years; P value not reported). This approximates one extra ovarian cancer for roughly 8,300 women taking hormone therapy each year.<br><br>Regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increase risk of ovarian cancer.<br><br>Secondary:<br>Not reported |
| Jaakkola et al.[139] (2012)<br><br>Estrogen plus progesterone | Cohort, PRO<br><br>Women who had used estrogen/ progesterone | N=243,857<br><br>Duration not specified | Primary:<br>Incidence of cervical precancerous or cancerous lesions | Primary:<br>Among patients receiving combination hormone therapy, there were 210 patients with squamous lesions (178 precancerous, 32 cancerous) and there were 79 patients with glandular lesions (14 precancerous, 65 adenocarcinomas). The use of combination hormone therapy was not |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Patient population was compared to background population. | therapy in 1994 to 2008 for ≥6 months, ≥50 years of age were identified | | Secondary<br>Not reported | associated with incidence of precancerous lesions, but the risk for squamous cell carcinoma decreased (standardized incidence ratio, 0.41; 95% CI, 0.28 to 0.58) and that for adenocarcinoma increased (1.31; 95% CI, 1.01 to 1.67).<br><br>After use of combination hormone therapy for five years, the risk for squamous cell carcinoma decreased (standardized incidence ratio, 0.34; 95% CI, 0.16 to 0.65), and the risk for adenocarcinomas increased (1.83; 95% CI, 1.24 to 2.59).<br><br>Secondary:<br>Not reported |

*Estradot® is marketed in the United States as Vivelle-Dot®.
†Menorest® is marketed in the United States as Vivelle®.
‡Product is not available in the United States.
Drug regimen abbreviations: QD=once daily
Study design abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross-over
Miscellaneous abbreviations: 3MSE= Modified Mini-Mental State Examination, AIP=atherogenic index of plasma, AUC=area under the curve, BMD=bone marrow density, BP=blood pressure, CABG= coronary artery bypass graft, CBG=cortisol binding globulin, CEE=conjugated equine estrogen, CHD=coronary heart disease, CHF= congestive heart failure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, FI=fluctuation index, FSH= follicle-stimulating hormone, HDL-C= high-density lipoprotein cholesterol, HR=hazard ratio, HOMA-IR=homeostasis model assessment of insulin resistance, ICAM=intracellular adhesion molecule, IGF-1=insulin-like growth factor 1, IL-6=interleukin-6, LDL-C= low-density lipoprotein cholesterol, MI= myocardial infarction, MPA=medroxyprogesterone, OR=odds ratio, PCI= percutaneous coronary interventions, PE=pulmonary embolism, QCT=quantitative computed tomography, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SHBG=sex hormone binding globulin, TBG=thyroxine binding globulin, TC=total cholesterol, TG=triglyceride, VLDL-C=very-low-density lipoprotein cholesterol, VTE=venous thromboembolism, WHI=Women's Health Initiative, WHIMS=Women's Health Initiative Memory Study

**Additional Evidence**

Dose Simplification
Two studies demonstrated that continuous administration of hormone therapy was better tolerated than sequential administration, which led to an improvement in compliance. Doren et al. found that women who were treated with continuous estrogen and progestin therapy (estradiol 2 mg, estriol 1 mg, and norethisterone 1 mg) had better compliance than women who were treated sequentially with estradiol valerate 2 mg daily and medroxyprogesterone acetate 5 mg daily for 12 days of the month (93 vs 66%, respectively). The most frequent reason for discontinuation of therapy was uterine bleeding.[140] Eiken et al. found that the continuous administration of estradiol and norethisterone improved compliance compared to the sequential administration of the same product. The eight year compliance rate for the continuous combination regimen was 46% compared to 32% for the sequential regimen. The difference in compliance rates was due to monthly bleeding associated with the sequential regimen.[49]

Stable Therapy
Place et al. evaluated women whose menopausal symptoms were satisfactorily controlled on conjugated estrogens. Participants were randomly selected to continue with oral therapy or to switch to transdermal estradiol. The results showed that women who switched to transdermal therapy had similar relief of menopausal symptoms as the women who remained on oral conjugated estrogens.[86]

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 12. Relative Cost of the Estrogens**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Estradiol | tablet, topical emulsion, topical gel, topical spray, transdermal patch, vaginal cream, vaginal ring, vaginal tablet | Alora®, Climara®*, Divigel®, Elestrin®, Estrace®*, Estrasorb®, Estring®, Evamist®, Menostar®, Vagifem®, Vivelle-Dot® | $$-$$$$ | $-$$ |
| Estradiol acetate | tablet, vaginal ring | Femring®, Femtrace® | $$-$$$$ | N/A |

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Estradiol cypionate | injection | Depo-Estradiol® | $$ | N/A |
| Estradiol valerate | injection | Delestrogen®* | $$$$ | $$$-$$$$ |
| Estradiol and drospirenone | tablet | Angeliq® | $$$ | N/A |
| Estradiol and levonorgestrel | transdermal patch | Climara Pro® | $$$ | N/A |
| Estradiol and norethindrone | tablet, transdermal patch | Activella®*, Combipatch® | $$$ | $$ |
| Estradiol and norgestimate | tablet | Prefest® | $$-$$$ | N/A |
| Estrogens, conjugated | injection, tablet, vaginal cream | Premarin® | $$-$$$$ | N/A |
| Estrogens, conjugated, synthetic A | tablet | Cenestin® | $$-$$$ | N/A |
| Estrogens, conjugated, synthetic B | tablet | Enjuvia® | $$ | N/A |
| Estrogens, conjugated and medroxyprogesterone | tablet | Premphase®, Prempro® | $$$ | N/A |
| Estrogens, esterified | tablet | Menest® | $-$$$ | N/A |
| Estropipate | tablet | N/A | $$-$$$ | $ |
| Norethindrone and ethinyl estradiol | tablet | FemHRT®* | $$$ | X |

*Generic is available in at least one dosage form or strength.
N/A=Not available

## X. Conclusions

The estrogens are approved for the treatment of vasomotor symptoms associated with menopause, vulvar and vaginal atrophy, abnormal uterine bleeding, hypoestrogenism, prevention of postmenopausal osteoporosis, as well as for the palliative treatment of prostate and breast cancer.[1-34] They are available in a variety of dosage forms, including injectable, oral, topical, transdermal and vaginal preparations. Estradiol, estradiol valerate, estradiol/norethindrone and estropipate are available in a generic formulation.

The recommendations for the use of hormone therapy have changed since the Women's Health Initiative studies were published.[36-38,46-48,50-53,56,57] The use of hormone therapy was associated with an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis.[41,42] The long-term use of hormone therapy is no longer recommended for the prevention of chronic diseases, such as cardiovascular disease, cerebrovascular disease or dementia.[38,46,51,42] Hormone therapy may be considered for the prevention of osteoporosis when other therapies are not appropriate or when the benefits outweigh the risks.[37,46,48] Hormone therapy remains the most effective treatment for moderate-to-severe menopausal symptoms.[37,46,48,53,56]
It is recommended that the lowest possible dose be used for the shortest amount of time.[37,46,57,58] Vaginal formulations are recommended for women who only have symptoms of vulvar and vaginal atrophy.[37,46,47]
Systemic progestogen is required for endometrial protection of unopposed estrogen therapy.[37]

A variety of clinical trials have been conducted with the estrogens, which have evaluated efficacy, safety, tolerability, as well as pharmacokinetic and pharmacodynamic end points. Numerous studies have demonstrated a similar improvement in menopausal symptoms with the various estrogen preparations.[46,47,50,74,76,80,82-90,93-95,99-102,127]
There were no studies found in the medical literature that compared the continuous administration of a combination product versus the concomitant administration of the individual components. There is no evidence that natural estrogens are more or less hazardous than synthetic estrogens at equivalent doses.[1-34]

There is insufficient evidence to support that one brand estrogen is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand estrogen is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Alpha-Glucosidase Inhibitors
# AHFS Class 682002
# November 14, 2012

## I. Overview

Diabetes mellitus is a chronic condition which results in hyperglycemia. It is differentiated into 4 main classes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes; and 4) other types (drug- or chemical-induced, genetic defects in β-cell function or insulin action, and diseases of the exocrine pancreas). Type 2 diabetes is the most prevalent form of the disease in the United States. Inadequate glycemic control may lead to both acute and long-term complications, including microvascular and macrovascular events. There are a variety of oral and injectable antidiabetic agents currently available to treat this devastating disease.

The antidiabetic agents are categorized into nine different American Hospital Formulary Service (AHFS) classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The alpha-glucosidase inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The antihyperglycemic action of acarbose results from a competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolase enzymes. The antihyperglycemic action of miglitol results from a reversible inhibition of membrane-bound intestinal alpha-glucoside hydrolase enzymes. This enzyme inhibition leads to a delay in glucose absorption and subsequent lowering of postprandial hyperglycemia.[1,2]

The alpha-glucosidase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Acarbose is available in a generic formulation. This class was last reviewed in May 2010.

**Table 1. Alpha-Glucosidase Inhibitors Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Acarbose | tablet | Precose®* | acarbose |
| Miglitol | tablet | Glyset® | Glyset® |

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Alpha-Glucosidase Inhibitors**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[3] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[4] (2012)** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | Initial drug therapy<br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br>Advancing to dual combination therapy<br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.<br>• Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.<br>• It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.<br>• For all medications, consideration should also be given to overall tolerability.<br><br>Advancing to triple combination therapy<br>• Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.<br>• Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored |

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>
in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
<ul>
<li>In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.</li>
<li>Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.</li>
</ul>
Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations
<table>
<tr><td>Initial Drug Monotherapy</td><td colspan="5">Metformin</td></tr>
<tr><td>Efficacy (↓$HbA_{1c}$)</td><td colspan="5">High</td></tr>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonyl-urea</td><td>Metformin + thia-zolidinedione (TZD)</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor agonist</td><td>Metformin + insulin (usually basal)</td></tr>
<tr><td>Efficacy (↓$HbA_{1c}$)</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypo-glycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Oedema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td rowspan="2">Three Drug Combin-ations</td><td>Metformin + sulfonyl-urea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td>TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table>
</td></tr>
<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[5] (2012)</td><td>
<ul>
<li>Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.</li>
<li>Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.</li>
<li>It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.</li>
</ul>
</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for</td><td>
<u>Antihyperglycemic pharmacotherapy</u>
<ul>
<li>The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009</li>
</ul>
</td></tr>
</table>

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[6] (2011)** | American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[7]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology** | <u>Principles underlying the algorithm</u><br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[7] (2009)** | • Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br><u>Stratification by current $HbA_{1c}$</u><br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br><u>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%</u><br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • The following triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + GLP-1 receptor agonist + glinide.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>  ○ Metformin + DPP-4 inhibitor + glinide.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist.<br>  ○ Metformin + DPP-4 inhibitor.<br>  ○ Metformin + TZD.<br>  ○ Metformin + sulfonylurea.<br>  ○ Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>  ○ Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>  ○ Metformin + TZD.<br>  ○ Metformin + TZD + sulfonylurea.<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[8] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>  ○ Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>  ○ Initiate self-monitoring blood glucose levels.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>• First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>• After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>• Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>• Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>• Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[9] (2009)** | <u>DPP-4 inhibitors</u><br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br><u>TZDs</u><br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  o A body mass index ≥35 $kg/m^2$ in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI <35 $kg/m^2$, and thera$^{p}$y with insulin would have significant occupational implications or weight loss would |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | benefit other sig[n]ificant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  o A person prefers injecting insulin immediately before a meal<br>  o Hypoglycemia is a problem.<br>  o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>  o Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>  o Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>  o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>  o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>• Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[10] (2008)** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br><u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>  o The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>  o A sulfonylurea if metformin is not tolerated.<br>  o Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br><u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u><br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/m$^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  o Inadequate blood glucose control ($HbA_{1c}$ ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  o Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  o Continue with metformin and the sulfonylurea (and acarbose, |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | if used)<br>○ Review the use of the sulfonylurea if hypoglycemia occurs<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>○ Continue with metformin<br>○ Continue the sulfonylurea initially and discontinue if hypoglycemia occurs<br>• Consider combining pioglitazone with insulin therapy for:<br>○ Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>○ Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>○ Those who require assistance from a care taker or healthcare professional to administer their insulin injections<br>○ Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes<br>○ Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ is >9.0%. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>○ Immediate injection before a meal is preferred.<br>○ Hypoglycemia is a problem.<br>○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI):<br>**Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[11] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes[12] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br>Insulin<br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the alpha-glucosidase inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Alpha-Glucosidase Inhibitors[1,2]**

| Indication(s) | Acarbose | Miglitol |
|---|---|---|
| Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | ✔ | ✔ |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the alpha-glucosidase inhibitors are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the Alpha-Glucosidase Inhibitors[13]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| Acarbose | 0.5 to 2.0 | Negligible (% not reported) | Intestinal wall (extensive, % not reported) | Renal (2), Feces (51) | 2 |
| Miglitol | 100 | <4 | Hepatic (% not reported) | Renal (>95) | 2 |

## V. Drug Interactions

Significant drug interactions with the alpha-glucosidase inhibitors are listed in Table 5.

**Table 5. Significant Drug Interactions with the Alpha-Glucosidase Inhibitors[14]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Acarbose | 2 | Digoxin | Impaired digoxin absorption is suspected; therefore, serum digoxin concentrations may be reduced, decreasing its therapeutic effects. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

The most common adverse drug events reported with the alpha-glucosidase inhibitors are listed in Table 6.

**Table 6. Adverse Drug Events (%) Reported with the Alpha-Glucosidase Inhibitors[1,2]**

| Adverse Events | Acarbose | Miglitol |
|---|---|---|
| **Dermatologic** | | |
| Hypersensitive skin reactions | ✔ | - |
| Rash | ✔ | 4.3 |
| **Gastrointestinal** | | |
| Abdominal pain | 19 | 11.7 |
| Diarrhea | 31 | 28.7 |
| Flatulence | 74 | 41.5 |
| Ileus/subileus | ✔ | - |
| **Hepatic** | | |
| Fulminant hepatitis | - | - |
| Hepatitis | ✔ | - |
| Jaundice | ✔ | - |
| Transaminases increased | <4 | - |
| **Other** | | |
| Edema | ✔ | - |
| Low serum iron | - | 9.2 |

✔ Percent not specified.
- Event not reported.

## VII. Dosing and Administration

The usual dosing regimens for the alpha-glucosidase inhibitors are listed in Table 7.

**Table 7. Usual Dosing Regimens for the Alpha-Glucosidase Inhibitors[1,2]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| Acarbose | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 25 mg TID with meals; maintenance, 25 to 50 mg TID; maximum, 50 mg TID (≤60 kg) or 100 mg TID (>60 kg) | Safety and effectiveness in pediatric patients have not been established. | Tablet: 25 mg 50 mg 100 mg |
| Miglitol | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 25 mg TID with meals; maintenance, 50 mg TID; maximum, 100 mg TID | Safety and effectiveness in pediatric patients have not been established. | Tablet: 25 mg 50 mg 100 mg |

TID=three times daily

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the alpha-glucosidase inhibitors are summarized in Table 8.

**Table 8. Comparative Clinical Trials with the Alpha-Glucosidase Inhibitors**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Cardiovascular Outcomes Trials** | | | | |
| Chiasson et al.[15] (2003)<br><br>Acarbose 100 mg TID<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m$^2$ with impaired glucose tolerance test and a FPG 100 to 140 mg/dL | N=1,429<br><br>3.3 years (mean duration) | Primary:<br>Number of patients who developed major cardiovascular events<br><br>Secondary:<br>New cases of hypertension | Primary:<br>Fifteen patients receiving acarbose and 32 patients receiving placebo experienced any cardiovascular event. Acarbose was associated with a 49% RR reduction in the development of any cardiovascular event (HR, 0.51; 95% CI, 0.25 to 0.95; P=0.03) and a 2.5% absolute risk reduction.<br><br>There was a significant reduction in the risk of MI associated with acarbose treatment; one patient experienced a MI with acarbose and 12 patients with placebo (HR, 0.09; 95% CI, 0.01 to 0.72; P=0.02).<br><br>Five patients receiving acarbose experienced angina compared to 12 patients receiving placebo (P=0.13). Eleven patients receiving acarbose experienced revascularization procedures and 20 patients receiving placebo (P=0.18). One patient receiving acarbose experienced cardiovascular death compared to two patients receiving placebo (P=0.63). No patient receiving acarbose and two patients receiving placebo experienced congestive heart failure. Two patients receiving acarbose and four patients receiving placebo experienced a cerebrovascular event or stroke (P=0.51). One patient in each group experienced peripheral vascular disease (P=0.93).<br><br>Secondary:<br>Seventy eight (11%) of the 682 patients receiving acarbose developed hypertension compared to 115 (17%) of the 686 patients receiving placebo. There was a 34% RR decrease in the incidence of new hypertension cases associated with acarbose (HR, 0.66; 95% CI, 0.49 to 089; P=0.006) and a 5.3% absolute risk reduction.<br><br>Reduction in the risk of cardiovascular events (HR, 0.47; 95% CI, 0.24 to 0.90; P=0.02) and hypertension (HR, 0.62; 95% CI, 0.45 to 0.86; P=0.004) associated with acarbose was significant after adjusting for the major risk |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | factors. |
| **Diabetes Prevention Trials** | | | | |
| Chiasson et al.[16] (2002)<br><br>Acarbose 100 mg TID<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 40 to 70 years of age, with a BMI 25 to 40 kg/m$^2$, and impaired glucose tolerance test according to the WHO criteria, and a FPG 100 to 140 mg/dL | N=1,429<br><br>3.3 years (mean duration) | Primary:<br>The development of diabetes on the basis of a yearly oral glucose tolerance test<br><br>Secondary:<br>Not reported | Primary:<br>One hundred seventeen (17%) patients developed diabetes in the acarbose group compared to 178 (26%) patients in the placebo group (HR, 0.68; 95% CI, 0.54 to 0.85; P=0.0010), resulting in an absolute reduction of 8.7% and a relative reduction of 32.4% when a FPG of 7.0 mmol/L or greater was reported on two consecutive visits as the criterion for the development of diabetes.<br><br>When any two positive oral glucose tolerance tests with a two-hour plasma glucose of 11.1 mmol/L or greater, 105 (15%) patients converted to diabetes in the acarbose group compared to 165 (24%) patients in the placebo group (HR, 0.64; 95% CI, 0.4981 to 0.8129; P=0.003) for an absolute reduction of 8.7% and a relative reduction of 36.4%.<br><br>Based on one abnormal plasma glucose concentration, cumulative incidence of diabetes was 221 (32%) patients in the acarbose group and 285 (42%) patients in the placebo group (relative hazard, 0.75; 95% CI, 0.63 to 0.90; P=0.0015).<br><br>Probability of reverting to normal glucose tolerance over time was significantly higher in patients on acarbose than in those on placebo (P<0.001).<br><br>Secondary:<br>Not reported |
| Van de Laar et al.[17] (2006)<br><br>Acarbose<br><br>vs<br><br>placebo, metformin, diet | MA (5 trials)<br><br>Patients with impaired glucose tolerance or impaired fasting blood glucose | N=2,360<br><br>1 to 6 years | Primary:<br>Occurrence of type 2 diabetes<br><br>Secondary:<br>Cardiovascular morbidity and mortality, glycemic control, lipids, BP, body weight | Primary:<br>In the comparison of acarbose to placebo, the incidence of or conversion to type 2 diabetes was reduced (RR, 0.78; 95% CI, 0.68 to 0.90).<br><br>Neither acarbose nor metformin had significant effects on the incidence of type 2 diabetes when compared to one another. However, when compared to diet and exercise, acarbose had beneficial effects on the incidence of type 2 diabetes (RR, 0.40; 95% CI, 0.17 to 0.96).<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| and exercise, or both | | | | There were no significant effects on total mortality or mortality due to cardiovascular causes in trials comparing acarbose to placebo. In one trial (STOP-NIDDM), a decreasing effect on the incidence of cardiovascular disease as a combined end point (MI, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) was reported (RR, 0.47; 95% CI, 0.26 to 0.86).<br><br>Acarbose decreased PPG by 0.61 mmol/L (95% CI, 0.27 to 0.95) compared to placebo. In the EDIT study, acarbose significantly decreased FPG and PPG in comparison to placebo (P=0.0043 and P=0.0075, respectively). In comparison to metformin, acarbose showed a decreasing effect on PPG (1.40 mmol/L; 95% CI, 0.55 to 2.25). Similarly, acarbose vs diet and exercise also showed significant reductions in FPG and PPG (-1.37 [95% CI, -0.50 to -2.24] and -2.79 mmol/L [95% CI, -1.79 to -3.79]).<br><br>There were no significant effects on DBP and SBP in trials comparing acarbose to placebo. However, metformin showed significant decreases in both TC and DBP in comparison to acarbose (0.90 mmol/L [95% CI, 0.19 to 1.61] and 6 mm Hg [95% CI, 2.81 to 9.19], respectively).<br><br>Acarbose decreased body weight by 1.2 kg (95% CI, 0.5 to 1.8) and BMI by 0.3 $kg/m^2$ (95% CI, 0.1 to 0.5) compared to placebo. |
| **Type 2 Diabetes – Monotherapy** | | | | |
| Buse et al.[18] (1998)<br>PROTECT<br><br>Acarbose 25 to 50 mg TID<br><br>The dose remained at 50 mg TID, or the dose was increased to 100 mg TID, or a sulfonylurea was | MC, OL, PRO<br><br>Patients ≥21 years of age with type 2 diabetes who were inadequately controlled with either diet alone or diet and a sulfonylurea | N=6,142<br><br>28 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline PPG | Primary:<br>Mean $HbA_{1c}$ after 28 weeks was 8.41%. The mean change from baseline in $HbA_{1c}$ at trial end was -0.66% (P<0.001).<br><br>Secondary:<br>Mean PPG level was 208.1 mg/dL after 28 weeks of therapy. The mean PPG level decreased by 41 mg/dL at trial end (P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| added, or the dose of the sulfonylurea was increased. | | | | |
| Hwu et al.[19]<br>Asian Acarbose Study Group (2003)<br><br>Acarbose<br>50 mg TID for 6 weeks, titrated up to 100 mg TID for 12 weeks<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Asian patients 35 to 70 years of age with type 2 diabetes receiving insulin with inadequate control, an $HbA_{1c}$ 8.0 to 11.0%, requiring ≥2 injections of intermediate insulin per day, and a BMI ≤35 kg/m$^2$ | N=117<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Changes in baseline FPG, PPG, and lipids | Primary:<br>$HbA_{1c}$ improved with acarbose (-0.5±1.3%) and worsened with placebo (0.2±1.2%). The comparison between the two treatments showed a difference of -0.69% (95% CI, -1.18 to -0.20; P=0.008) in favor of acarbose.<br><br>Secondary:<br>FPG decreased with acarbose by trial end, but there was not a significant difference between placebo (0.04 mmol/L; 95% CI, -1.28 to 1.66; P=0.094).<br><br>Differences between the two treatments were significant for the PPG data (-1.89 mmol/L; 95% CI, -3.50 to -0.28; P=0.029), but was not significant for the two-hour post-prandial data (-1.83 mmol/L; 95% CI, -3.67 to 0.00; P=0.051).<br><br>There were no differences between the two treatments, from baseline to trial end, for TG, TC, and LDL-C (P=0.378, P=0.935, P=0.294, respectively). There was a small decrease in HDL-C with acarbose (P=0.049). |
| Josse et al.[20]<br>(2003)<br><br>Acarbose 50 to 100 mg TID<br><br>vs<br><br>placebo | DB, PC, RCT<br><br>Patients >65 years of age with type 2 diabetes treated with diet alone | N=192<br><br>1 year | Primary:<br>Change in $HbA_{1c}$, FPG, fasting insulin, relative insulin sensitivity, and glucose; insulin incremental AUC<br><br>Secondary:<br>Not reported | Primary:<br>Differences in the change from baseline in $HbA_{1c}$ between acarbose and placebo was -0.6% (P<0.05). Acarbose 100 mg TID resulted in a greater $HbA_{1c}$ treatment effect compared to acarbose 50 TID (-0.9 vs -0.2%; P value not reported).<br><br>Change in FPG level was greater with acarbose compared to placebo (-0.7 mmol/L; P<0.05).<br><br>Change in fasting insulin was -9±4 and -9 pmol/L with acarbose and placebo; the difference was not significant (P value not reported).<br><br>Acarbose showed a significant reduction in glucose and insulin incremental AUC compared to placebo (glucose, -2.1 mmol/h l [P<0.05] |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | and insulin, -45 pmol/h l; [P<0.05]).<br><br>Acarbose showed a significant reduction in relative insulin resistance compared to placebo (–0.8; P<0.05).<br><br>Secondary:<br>Not reported |
| Lam et al.[21] (1998)<br><br>Acarbose 50 mg TID for 4 weeks, titrated up to 100 mg TID for 20 weeks<br><br>vs<br><br>placebo | DB, MC, RCT<br><br>Patients with type 2 diabetes, BMI <30 kg/m$^2$, $HbA_{1c}$ 8.4 to 10.8%, and on maximal doses of glibenclamide* or gliclazide† and metformin for ≥6 months | N=90<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, PPG, insulin levels, and fasting lipid levels<br><br>Secondary:<br>Not reported | Primary:<br>Acarbose was associated with greater reductions in $HbA_{1c}$ (-0.5±0.2 vs 0.1±0.2%; P=0.038), one-hour PPG (-2.3 ±0.4 vs 0.7±0.4 mmol/L; P<0.001) and body weight (-0.54±0.32 vs 0.42±0.29 kg; P<0.05).<br><br>No significant differences between the two treatments with regards to FPG, lipids, or fasting and postprandial insulin levels (P values not reported).<br><br>Gastrointestinal symptoms were the most common side effects with flatulence occurring the most compared to placebo (P<0.05).<br><br>Secondary:<br>Not reported |
| Lin et al.[22] (2003)<br><br>Acarbose 100 mg TID<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Asian patients 35 to 70 years of age with type 2 diabetes for ≥3 months, $HbA_{1c}$ 7.0 to 10.0%, stable body weight (≤35 kg), and uncontrolled by diet and sulfonylureas | N=69<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline blood glucose (FPG and PPG), serum insulin (fasting and one-hour postprandial), urinary glucose, safety | Primary:<br>Acarbose was associated with significantly greater reductions in $HbA_{1c}$ (-0.91 vs 0.13%; P=0.0018) and PPG levels (-2.84 vs 0.28 mmol/L; P=0.002).<br><br>Secondary:<br>There were no significant differences between the treatment groups regarding changes in FPG (P=0.1941), fasting insulin (P=0.5003), insulin PPG (P=0.2799), urinary glucose (P value not reported), and body weight (P value not reported).<br><br>Change in blood glucose (FPG and PPG) was significant for acarbose compared to placebo (P=0.0020).<br><br>Adverse events occurred with similar frequency with both treatments except for drug-related gastrointestinal side effects with acarbose (48.5 vs |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | 12.5%; P value not reported). |
| Mori et al.[23] (2011)<br><br>Acarbose 300 mg/day, administered on 2 of 4 days<br><br>vs<br><br>no treatment | SA<br><br>Adults with type 2 diabetes | N=10<br><br>4 days | Primary:<br>Glucose fluctuations<br><br>Secondary:<br>Not reported | Primary:<br>During treatment, significant decreases in median of 24-hour mean blood glucose (22.48 vs 32.78 mg/dL; P=0.004), 24-hour mean blood glucose fluctuations (453.27 vs 677.05 mgh/dL; P=0.002), and mean amplitude of glycemic excursions (65.00 vs 97.09; P=0.010) were achieved with acarbose compared to no treatment.<br><br>Secondary:<br>Not reported |
| Jian-bin et al.[24] (2011)<br><br>Acarbose 50 mg TID<br><br>vs<br><br>no treatment<br><br>All patients received existing insulin regimens.<br><br>After an initial 3 day continuous glucose monitoring test, patients with mean amplitude of glycemic excursions >3.4 mmol/L received acarbose for 2 weeks (high group); patients | PRO<br><br>Type 2 diabetics receiving premixed insulin BID for >3 consecutive months and $HbA_{1c}$ <6.5% | N=106 (includes 20 control subjects who had normal glucose regulation)<br><br>3 days | Primary:<br>Glycemic variability, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>Among the 86 patients, the mean amplitude of glycemic excursions and mean of daily differences of type 2 diabetes groups were all higher compared to control patients (P<0.01).<br><br>Twenty-four percent of patients in the high group (n=11) had a total of 13 hypoglycemic events, and 10 of the 13 events occurred at night. Five percent of patients in the low group (n=2) had a total of two hypoglycemic events, and both occurred at night (24 vs 5%; P<0.01). Mean amplitude of glycemic excursion value was correlated with hypoglycemia value and two-hour PPG value (P<0.05).<br><br>After further treatment with acarbose and second continuous glucose monitoring, mean amplitude of glycemic excursions and mean of daily differences values in the high group were all significantly decreased (40%; P<0.01, and 15%; P<0.05, respectively), but remained higher compared to control patients (P<0.05). Two percent of patients (n=1) had a total of one hypoglycemic event.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| with values <3.4 mmol/L did not receive additional treatment (low group). | | | | |
| Feinbock et al.[25] (2003)<br><br>Acarbose 50 to 200 mg TID<br><br>vs<br><br>glimepiride 1 to 6 mg QD | MC, OL, PG, RCT<br><br>Patients from 36 to 80 years of age with type 2 diabetes uncontrolled on diet alone, with an $HbA_{1c}$ ≥7.8%, and BMI 24 to 35 kg/m$^2$ | N=219<br><br>20 weeks | Primary:<br>Number of responders in each group (defined as a FPG ≤7.8 mmol/L at the final visit)<br><br>Secondary:<br>Changes in $HbA_{1c}$, weight, PPG, and C-peptide levels from baseline | Primary:<br>Glimepiride treatment was associated with a significant responder rate compared to acarbose, 61 vs 34% respectively (P<0.001).<br><br>Glimepiride resulted in significant decreases in $HbA_{1c}$ (2.5±2.2%) as compared to acarbose (1.8±2.2%; P=0.014).<br><br>Secondary:<br>FPG levels were significantly decreased with glimepiride as compared to acarbose (2.6±2.6 vs 1.4±2.8 mmol/L; P=0.004).<br><br>There was a greater reduction in $HbA_{1c}$ in the glimepiride group (2.5±2.2%) compared to the acarbose group (1.8±2.2%; P=0.014).<br><br>Decreased glucose response to breakfast was significant for glimepiride compared to acarbose (P=0.0001).<br><br>Weight loss was observed in the acarbose group (P=0.001) and glimepiride group (P=0.8) from baseline.<br><br>C-peptide levels were higher in the glimepiride group compared to the acarbose group at study end point (5.44±2.26 vs 4.57±1.93 ng/mL; P=0.0004; intra-individual difference, 0.53 ±1.7 vs -0.31 ±1.72 ng/mL; P=0.002). |
| van de Laar et al.[26] (2004)<br><br>Acarbose titrated to 100 mg TID<br><br>vs | DB, RCT<br><br>Newly diagnosed patients with type 2 diabetes between 40 to 70 years of age and a FPG level between 6.7 and | N=96<br><br>30 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change in fasting and postload blood glucose and insulin | Primary:<br>Both treatment groups showed a decrease in $HbA_{1c}$. The $HbA_{1c}$ change from baseline for the acarbose group was -1.1 vs -1.8% for the tolbutamide group. The difference between the groups was 0.6% in favor of tolbutamide (90% CI, 0.3 to 0.9 and 95% CI, 0.2 to 1.0).<br><br>Secondary:<br>Difference in mean decrease of FPG was 1.0 mmol/L in favor of |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| tolbutamide titrated 2,000 mg daily in 3 divided doses | 20.0 mmol/L after an 8-week dietary treatment period | | levels, plasma lipids, tolerability | tolbutamide (95% CI, 0.3 to 1.7).<br><br>No significant differences were seen in postload blood glucose, fasting and postload insulin levels, or lipids. |
| Wagner et al.[27] (2006)<br><br>Acarbose 100 mg TID<br><br>vs<br><br>aerobic/anaerobic exercise group training for 50 minutes 3 times weekly<br><br>vs<br><br>acarbose 100 mg TID plus exercise | RCT<br><br>Patients 45 to 60 years of age with type 2 diabetes for ≥3 months, $HbA_{1c}$ <7.5%, and BMI 25 to 30 kg/m$^2$ | N=62<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$, insulin sensitivity (M value), regional fat distribution, $Vo_{2max}$ (a measure of physical fitness)<br><br>Secondary:<br>Not reported | Primary:<br>At trial end, acarbose resulted in no effects on $HbA_{1c}$, FPG, M value, BMI, body composition, or $Vo_{2max}$. However, fasting plasma proinsulin level was significantly reduced ($P$=0.009).<br><br>With exercise there were significant reductions in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat area. Although $Vo_{2max}$ was unchanged, there was an increase in maximal workload ($P$=0.005) and in the M value ($P$=0.017). $HbA_{1c}$ was unchanged.<br><br>Acarbose plus exercise resulted in significant decreases in BMI, waist circumference, total and truncal fat, and total and intra-abdominal fat. Maximal workload, $Vo_{2max}$, and M values were all increased ($P$=0.028, $P$=0.046, and $P$=0.002, respectively). Additionally, fasting plasma proinsulin levels were significantly reduced ($P$=0.013), as well as $HbA_{1c}$ ($P$ value not reported).<br><br>Secondary:<br>Not reported |
| de Luis Roman et al (abstract).[28] (2004)<br><br>Miglitol 50 mg BID for 1 week, followed by 50 mg TID | OL<br><br>Patients with type 2 diabetes inadequately controlled ($HbA_{1c}$ >7.5%) on sulfonylureas and insulin | N=33<br><br>3 months | Primary:<br>Change in weight, height, BMI, SBP, DBP, $HbA_{1c}$, number of episodes of peripheral hypoglycemia, basal glucose, albuminuria, TC, LDL-C, HDL-C, TG, and transaminases<br><br>Secondary: | Primary:<br>Blood glucose and $HbA_{1c}$ decreased 4.8 and 5.8%, respectively.<br><br>There was a decrease in the number of hypoglycemia episodes (39.4% previous quarter vs 3% during the miglitol quarter).<br><br>The required dose of sulfonylureas decreased (86.2±24.3 vs 64.6 ±21.9 mg/day; $P$<0.05).<br><br>TC, HDL-C, and LDL-C were not modified. There was a reduction in TG from 145.2 ±111.0 to 133.1±79.0 mg/dL ($P$<0.05).<br><br>Fifteen percent of patients experienced digestive discomfort, which disappeared two or three weeks after beginning the treatment. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | Not reported | Secondary:<br>Not reported |
| Aoki et al.[29] (2007)<br><br>Miglitol, administered prior to breakfast<br><br>vs<br><br>miglitol, administered 15 minutes after the start of breakfast<br><br>vs<br><br>miglitol, administered 30 minutes after the start of breakfast<br><br>vs<br><br>placebo | XO<br><br>Adult patients with type 2 diabetes, BMI 26.7 kg/m$^2$ (mean), $HbA_{1c}$ 9.3% (mean), and an average duration of diabetes of 7.4 years | N=13<br><br>180 minutes | Primary:<br>Effect of plasma glucose at 0, 30, 60, 120, and 180 minutes after breakfast; effect on serum insulin<br><br>Secondary:<br>Not reported | Primary:<br>At 30 and 60 minutes, plasma glucose levels were significantly decreased in those who took miglitol just before breakfast compared to control ($P$<0.05).<br><br>At 60 and 120 minutes, plasma glucose levels were significantly decreased in those taking miglitol 15 minutes after breakfast ($P$<0.05) while those taking miglitol 30 minutes after breakfast had significant reductions at 120 and 180 minutes ($P$<0.05) compared to control.<br><br>There were no significant differences between groups.<br><br>The AUC of serum insulin was lower with all three groups compared to control.<br><br>Secondary:<br>Not reported |
| Johnston el al.[30] (1998)<br><br>Miglitol 25 to 50 mg TID<br><br>vs<br><br>glyburide 1.25 to 20 mg QD | DB, MC, PC, PG, RCT<br><br>Patients ≥60 years of age with type 2 diabetes treated with diet alone for ≥12 weeks, $HbA_{1c}$ 6.5 to 10.0%, and FPG >140 mg/dL | N=411<br><br>1 year | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline plasma glucose, serum insulin, and TG | Primary:<br>Mean placebo-subtracted $HbA_{1c}$ reduction from baseline was -0.50% with miglitol 25 mg TID ($P$<0.05 vs glyburide), -0.41% with miglitol 50 mg TID ($P$<0.05 vs glyburide), -0.93% for glyburide QD, and -0.01% for placebo ($P$<0.05 vs all active treatments).<br><br>Secondary:<br>Changes in mean plasma glucose (AUC) were +716 mg·min/dL with placebo ($P$<0.05 vs all active treatments), -3,361 mg·min/dL with miglitol 25 mg TID, -5,462 mg·min/dL with miglitol 50 mg TID, and -3,615 |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>placebo | | | | mg·min/dL with glyburide (*P*=0.0001 for miglitol 50 mg TID vs placebo).<br><br>Postprandial insulin levels were significantly greater with glyburide compared to placebo and miglitol (*P*<0.01).<br><br>Mean changes from baseline to end point for fasting TG were 1.01 with placebo and miglitol 25 mg TID, 0.98 with miglitol 50 mg TID, and one with glyburide (*P*=0.573 for miglitol 50 mg vs placebo).<br><br>Mean changes from baseline to end point for TG (AUC) were 1.01 with placebo, 1.03 with miglitol 25 mg TID, 1.00 with miglitol 50 mg TID, and 1.06 with glyburide (*P*=0.8559 miglitol 50 mg TID vs placebo).<br><br>Hypoglycemia, weight gain, and routine and serious cardiovascular events were more frequent in the glyburide group (*P*<0.05 vs placebo and miglitol). |
| Tsujino et al[31]<br><br>Acarbose 50 mg, administered before each meal on day 2<br><br>vs<br><br>miglitol 100 mg, administered before each meal on day 2<br><br>Alternative treatments were administered on day 3 in a XO design. | RCT, XO<br><br>Patients 20 to 79 years of age with type 2 diabetes, taking α-glucosidase inhibitors without any other antidiabetic medications | N=10<br><br>4 days | Primary:<br>Glucose variability<br><br>Secondary:<br>Not reported | Primary:<br>No significant differences in regard to the range of increase in glucose levels from baseline to peak, time to peak PPG levels from the preprandial period, and AUC for glycemic variability from the preprandial period to three hours after each meal between the two treatments were observed. The range of increase in glucose levels at 30 minutes (0.4 vs 30.7 mg/dL; *P*<0.0001) and 60 minutes (32.8 vs 67.5 mg/dL; *P*<0.0001) after lunch and 30, 60, and 90 minutes after dinner (3.3 vs 22.2 mg/dL; *P*=0.0249, 36.6 vs 67.5 mg/dL; *P*<0.0001, and 60.5 vs 81.6 mg/day; *P*=0.0073, respectively) were significantly smaller with miglitol compared to acarbose.<br><br>Secondary:<br>Not reported |
| van de Laar et al.[32] (2005) | MA (41 trials) | N=8,130 | Primary:<br>Mortality, | Primary:<br>There was only limited data on mortality, morbidity, and quality of life. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| α-glucosidase inhibitor monotherapy | Patients with type 2 diabetes who received no other antidiabetic medication | ≥12 weeks | morbidity, quality of life, glycemic control, insulin, or C-peptide levels, lipids, body weight, safety<br><br>Secondary:<br>Not reported | Three trials reported mortality outcomes and found no differences between treatments.<br><br>Acarbose demonstrated an effect on glycemic control compared to placebo: $HbA_{1c}$, -0.8% (95% CI, -0.9 to -0.7); FPG, -2.3 mmol/L (95% CI, -2.7 to -1.9); and post-load glucose, -2.3 mmol/L (95% CI, -2.7 to -1.9). The effect on $HbA_{1c}$ from acarbose 50 to 300 mg TID was not dose-dependent. There seemed to be a dose dependency with miglitol in regards to $HbA_{1c}$: miglitol 25, 50, 100, and 200 mg TID decreased $HbA_{1c}$ by 0.46, 0.58, 0.79, and 1.26%, respectively.<br><br>A decreasing effect on post-load insulin was found.<br><br>There were no clinically relevant effects on lipids or body weight found.<br><br>Adverse events were generally of gastrointestinal origin and dose dependent.<br><br>Secondary:<br>Not reported |
| Bolen et al.[33] (2007)<br><br>Biguanides<br><br>vs<br><br>meglitinides<br><br>vs<br><br>TZDs<br><br>vs<br><br>α-glucosidase inhibitors | MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)<br><br>Patients with type 2 diabetes | N=136 (articles on intermediate outcomes)<br><br>N=167 (articles on adverse events)<br><br>N=68 (articles on microvascular outcomes and mortality)<br><br>Duration | Primary:<br>Intermediate outcomes: $HbA_{1c}$, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes<br><br>Secondary:<br>Adverse events: hypoglycemia, gastrointestinal problems, | Primary:<br>Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in $HbA_{1c}$ level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.<br><br>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.<br><br>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.<br><br>Most agents except metformin increased body weight by 1 to 5 kg. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>second-generation sulfonylureas | | varied | congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events | In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; *P*<0.05).<br><br>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).<br><br>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.<br><br>Secondary:<br>According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).<br><br>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.<br><br>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.<br><br>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents. |
| Saenz et al.[34] (2005)<br><br>Metformin | MA (29 RCTs)<br><br>Adult patients with type 2 diabetes | N=5,259<br><br>≥3 months | Primary:<br>Incidence of any diabetes-related outcomes (sudden | Primary:<br>Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (*P*=0.009) and for all-cause mortality (*P*=0.03). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| monotherapy<br><br>vs<br><br>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin | | | death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality<br><br>Secondary:<br>Changes in $HbA_{1c}$, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal | Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (*P*=0.004), diabetes-related death (*P*=0.03), all cause mortality (*P*=0.01), and MI (*P*=0.02).<br><br>Secondary:<br>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for $HbA_{1c}$ when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | plasma flow | |
| Richter et al.[35] (2006)<br><br>Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)<br><br>or<br><br>pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)<br><br>Some studies had more than one treatment arm. | MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | 22 trials<br><br>N=6,200 randomized to pioglitazone treatment (total N not reported)<br><br>24 weeks to 34.5 months | Primary:<br>Patient-oriented outcomes including mortality, morbidity and adverse effects<br><br>Secondary:<br>Health-related quality of life and $HbA_{1c}$ | Primary:<br>Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; *P*=0.095).<br><br>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; *P*=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; *P*=0.007).<br><br>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 $kg/m^2$. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (*P* value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; *P*<0.00001) when results from 18 trials were pooled.<br><br>Secondary:<br>No study investigated health-related quality of life.<br><br>Active glucose-lowering compounds like metformin, glibenclamide‡, |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | gliclazide* or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to pioglitazone treatment (*P* values not reported). |
| Monami et al[36] (2008)<br><br>Metformin<br><br>vs<br><br>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists | MA<br><br>Patients with type 2 diabetes mellitus | N=7,890 (27 RCT)<br><br>Variable duration | Primary:<br>Reduction in $HbA_{1c}$ at 16 to 36 months<br><br>Secondary:<br>Not reported | Primary:<br>Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in $HbA_{1c}$ by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.<br><br>In direct comparisons, sulfonylureas led to a greater reduction in $HbA_{1c}$ (0.17%; 95% CI, 0.16 to 0.18; *P*<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.<br><br>Secondary:<br>Not reported |
| **Type 2 Diabetes – Combination Therapy** | | | | |
| Halimi et al.[37] (2000)<br><br>Acarbose 50 to 100 mg TID and metformin 850 mg BID to TID<br><br>vs<br><br>metformin 850 mg BID to TID and placebo | DB, PC, PG, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes, BMI 25 to 35 $kg/m^2$, having poor glycemic control despite receiving metformin ≥2 months before the study start | N=152<br><br>6 months | Primary:<br>$HbA_{1c}$ at trial end<br><br>Secondary:<br>Blood glucose, insulin profiles, TG | Primary:<br>Mean difference in $HbA_{1c}$ from baseline to trial end was -0.7±1.2% with acarbose compared to 0.2±1.3% with placebo (*P*=0.0001).<br><br>Patients were classified as responders if their $HbA_{1c}$ values at trial end were <7.0% or had decreased by <15% relative to baseline. The total numbers of responders were 25 of 49 (42%) patients receiving acarbose and 12 of 70 (17%) patients receiving placebo (*P*=0.002).<br><br>Secondary:<br>Mean difference in the fasting blood glucose level from baseline to trial end was -1.0±2.8 mmol/L with acarbose compared to 1.3±2.8 mmol/L with placebo (*P*=0.0001).<br><br>Mean difference in two-hour PPG level from baseline to trial end was -1.4±3.8 mmol/L with acarbose compared to 1.1±3.5 mmol/L with placebo (*P*=0.0001).<br><br>Mean changes between acarbose compared to placebo for TG, fasting and postprandial serum insulin were not significant (P value not significant). |
| Phillips et al.[38] | DB, MC, PC, PG, | N=83 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (2003)<br><br>Acarbose 50 mg to 100 mg BID and metformin (existing therapy)<br><br>vs<br><br>metformin (existing therapy) and placebo | RCT<br><br>Patients ≥40 years of age with type 2 diabetes for ≥6 months, BMI 25 to 35 kg/m$^2$, $HbA_{1c}$ 7.0 to 10.0% at screening week and 6.8 to 10.2% at baseline, and inadequately controlled by metformin | 24 weeks | Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG | Mean $HbA_{1c}$ increased with placebo from 7.82±0.83% at baseline to 8.10±1.06% at week 12 and 8.50±1.44% at trial end. The mean increase after 24 weeks was 0.68±1.17%, with a significant overall time effect (P=0.0001).<br><br>With acarbose, mean $HbA_{1c}$ decreased from 8.02±0.85% at baseline to 7.78±1.00% at week 12 (P=0.0261). At the trial end, mean $HbA_{1c}$ increased to 7.97±1.10%. There was no significant overall time effect for acarbose (P value not reported).<br><br>Adjusted least square means for the change in $HbA_{1c}$ from baseline to trial end showed a decrease of 0.16±0.18% with acarbose compared to an increase of 0.86±0.16% with placebo. There was a significant difference between the treatment groups of 1.02% (95% CI, 0.543 to 1.497; P=0.0001).<br><br>Secondary:<br>Mean FPG levels increased with placebo from baseline (9.41±1.99 mmol/L) to week four (10.06±2.43 mmol/L) to trial end (10.77±3.39 mmol/L). The levels only changed slightly with acarbose.<br><br>Mean FPG increases were 1.36±2.88 mmol/L with placebo and 0.08±1.98 mmol/L with acarbose. The adjusted least square means showed increase at trial end with both treatments of 0.34±0.42 mmol/L with acarbose vs 1.48±0.39 mmol/L with placebo, with a significance of 1.132 mmol/L between the two treatments (95% CI, 0.056 to 2.208; P=0.0395). |
| Bayraktar et al.[39] (1996)<br><br>Acarbose 50 to 100 mg TID and a sulfonylurea<br><br>vs<br><br>metformin 500 mg TID and a | RCT, XO<br><br>Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, $HbA_{1c}$ >8.5%, FPG>7.7 mmol/L, or a PPG>10 mmol/L on maximum doses of gliclazide† (240 mg | N=18<br><br>20 weeks | Primary:<br>Changes in FPG, PPG, $HbA_{1c}$, TG, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline<br><br>Secondary:<br>Not reported | Primary:<br>Mean FPG, PPG, and $HbA_{1c}$ decreased at the end of each combination treatment period as compared with baseline levels (P<0.05).<br><br>PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05).<br><br>There was a significant decrease between pre- and posttreatment 2-hour PPG levels in each group (-5.3±0.4 for acarbose vs -2.9±0.3 for metformin; P<0.05). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| sulfonylurea | daily) | | | There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant.<br><br>Secondary:<br>Not reported |
| Bao et al.[40] (2010)<br><br>Glipizide XL<br><br>vs<br><br>glipizide XL plus acarbose | AC, OL, RCT<br><br>Newly diagnosed type 2 diabetics, 30 to 70 years of age, with $HbA_{1c}$ 7.0 to 9.8%, and no prior use of antidiabetic medications | N=40<br><br>8 weeks | Primary:<br>Glycemic control, improvements in insulin secretion and sensitivity, glycemic variability, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>After eight weeks, FPG, two-hour post-oral glucose tolerance test plasma glucose, mean blood glucose, $HbA_{1c}$, glycated albumin, and HOMA-IR were significantly decreased with both treatments. HOMA-B increased significantly compared to baseline (P<0.01 for both). Compared to glipizide XL, combination therapy had significantly lower mean blood glucose and HOMA-IR values after eight weeks (P<0.05 for both). Mean changes in mean blood glucose, $HbA_{1c}$, and glycated albumin were all greater with combination therapy compared to monotherapy, with only differences in mean blood glucose reaching significant. The overall glucose-lowering and -stabilizing effects were more pronounced with combination therapy.<br><br>Over the duration of the trial, the decreases in mean amplitude of glycemic excursions and $AUC_{postprandial\ incremental}$ were significant with both treatments (P<0.01). There was also a significant decrease in mean of daily differences with combination therapy compared to baseline (P<0.01). Patients receiving combination therapy had significantly lower mean of daily differences, mean amplitude of glycemic outcomes, and $AUC_{postprandial\ incremental}$ values compared to patients receiving monotherapy after eight weeks (P<0.05 for all).<br><br>There were no significant between-group differences in either the frequency or the duration of hypoglycemia. The mean duration of hypoglycemia was 88.8±84.7 minute per event with monotherapy and 176.3±123.5 minute per event with combination therapy (P=0.114). Patients receiving monotherapy had 0.7±0.4 events per day compared to 0.8±0.4 events per day in patients receiving combination therapy (P=0.612). There was no difference in total instances of severe hypoglycemia reported.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Not reported |
| Lopez-Alvarenga et al.[41] (1999)<br><br>Acarbose 100 mg TID, chlorpropamide 500 mg daily, and metformin 1,200 mg daily<br><br>vs<br><br>NPH insulin at bedtime, chlorpropamide 500 mg daily, and metformin 1,200 mg daily<br><br>vs<br><br>chlorpropamide (500 mg daily), metformin (1,200 mg daily), and placebo | DB, RCT, XO<br><br>Patients with type 2 diabetes from 35 to 70 years of age with BMI 23 to 35 kg/m$^2$, with a FPG >8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months | N=46<br><br>42 weeks | Primary:<br>Change in FPG from baseline, body weight, $HbA_{1c}$, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area)<br><br>Secondary:<br>Not reported | Primary:<br>Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003).<br><br>Changes in $HbA_{1c}$ from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008).<br><br>Changes in body weight were not significant in any group (P=0.2 vs baseline).<br><br>Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02).<br><br>Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24).<br><br>Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94).<br><br>Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02).<br><br>Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43).<br><br>Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin.<br><br>Secondary:<br>Not reported |
| Nemoto et al.[42] (2011) | DB, PC, RCT<br><br>Patients ≥20 years | N=107<br><br>12 weeks | Primary:<br>Change in baseline PPG and $HbA_{1c}$ | Primary:<br>The mean decrease in PPG with miglitol was significantly larger compared to placebo (-60.3±70.1 vs 5.1±68.2 mg/dL; P<0.001). The |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Miglitol 50 mg TID<br><br>vs<br><br>placebo<br><br>All patients received existing insulin regimens. | of age with type 2 diabetes receiving insulin therapy, plasma glucose level at either 1 or 2 hours after a meal was ≥180 mg/dL, and $HbA_{1c}$ ≥6.5% | (plus an additional 4 to 10 week observation period) | Secondary:<br>Safety | decrease in plasma glucose AUC was significantly larger with miglitol compared to placebo (-102.8±122.2 vs 8.7±121.1 mgh/dL; P<0.001).<br><br>Miglitol exhibited a significantly lower $HbA_{1c}$ compared to placebo from week eight to trial end. The decrease from baseline in $HbA_{1c}$ at week 12 was significantly greater with miglitol compared to placebo (-0.37±0.68 vs 0.04±0.56%; P<0.001).<br><br>Secondary:<br>The total incidence of adverse events was 78.5 and 76.0% with miglitol and placebo. Adverse events with high incidence included flatulence (20.6 vs 12.0%), abdominal distension (15.0 vs 4.0%), diarrhea (14.0 vs 4.0%), and hypoglycemia (39.3 vs 35.0%). The incidences of abdominal distention and diarrhea were significantly higher with miglitol (P<0.05 for both). All hypoglycemic events were mild and improved without treatment, by ingestion of glucose, supplements, or meals. |
| Hsieh et al.[43] (2011)<br><br>Miglitol 50 mg TID, titrated up to 100 mg TID<br><br>vs<br><br>placebo<br><br>Patients received existing sulfonylurea regimens. | DB, MC, PC, RCT<br><br>Chinese patients >20 years of age with type 2 diabetes, FPG 100 to 240 mg/dL, $HbA_{1c}$ 6.5 to 10.0%, history of uncontrolled type 2 diabetes despite prior nutrition therapy; and stable dosing with a sulfonylurea for ≥8 weeks | N=105<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, PPG, and post-prandial serum insulin; safety | Primary:<br>Mean change in $HbA_{1c}$ with miglitol was -0.85±0.12% compared to -0.19±0.11% with placebo (P<0.001).<br><br>Secondary:<br>No significant differences in the changes in FPG and post-prandial serum insulin were observed (P=0.052 and P=0.364).<br><br>There was a significant difference in the change in PPG between the two treatments (P<0.001).<br><br>Among the population, 49 (94.2%) patients receiving miglitol and 42 (79.3%) patients receiving placebo experienced at least one adverse event during the trial. A total of 59 and 39 adverse events occurred with miglitol and placebo, respectively. The most frequently reported adverse events were abdominal discomfort, diarrhea, hypoglycemia, and other; and there were no differences in the incidences of these events between the two treatments. |
| Standl et al.[44] (2001) | DB, MC, PC, PG, RCT | N=154<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>Miglitol produced a significant reduction in $HbA_{1c}$ (-0.55%; P=0.04) and PPG (-2.6 mmol/L; P=0.0009) compared to placebo. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Miglitol 25 mg to 100 mg TID, glibenclamide* 3.5 to 5 mg BID to QID, and metformin 500 to 850 mg daily<br><br>vs<br><br>glibenclamide* 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and placebo | Patients 30 to 70 years of age with type 2 diabetes for ≥3 years; $HbA_{1c}$ ≥7.5 to ≤10.5%; BMI ≤35 kg/m$^2$; stable body weight over the previous 3 months; and inadequately controlled on combination therapy of diet, glibenclamide* and metformin | | Secondary:<br>FPG, PPG, fasting and postprandial serum insulin, TG, urinary glucose | Secondary:<br>FPG decreased with miglitol and was almost unchanged with placebo; the difference was not significant (P=0.10).<br><br>Fasting insulin levels were unchanged with both treatments throughout the trial, with no significant difference between them (P=0.79).<br><br>Postprandial insulin decreased from baseline to trial end, but the difference between the groups was not significant (P=0.26).<br><br>Postprandial TG decreased slightly with miglitol and remained unchanged with placebo, and the difference was not significant (P=0.47). |
| Van Gaal et al.[45] (2001)<br><br>Miglitol 25 to 100 mg TID and metformin 500 mg TID or 850 mg BID or TID<br><br>vs<br><br>metformin 500 mg TID or 850 mg BID or TID and placebo | DB, MC, PC, PG, RCT<br><br>Patients 30 to 75 years of age with type 2 diabetes for ≥1 year, $HbA_{1c}$ ≥7.5 to ≤10.5%, BMI 23 to 40 kg/m$^2$, stable body weight over the previous 3 months, and whose diabetes was inadequately controlled by diet and metformin | N=152<br><br>32 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in FPG, PPG, serum insulin, fasting and one-hour postprandial TG levels | Primary:<br>There was a significant decrease in $HbA_{1c}$ with miglitol compared to placebo (-0.21 vs 0.22%; P=0.011).<br><br>Secondary:<br>PPG decreased with both treatments, but the reduction was more significant with miglitol (from 16.5±3.8 mmol/L at baseline to 13.8±5.0 mmol/L at trial end) compared to placebo (from 16.3±3.4 mmol/L at baseline to 15.7±3.8 mmol/L at trial end). The baseline adjusted means were 13.8 mmol/L with miglitol vs 15.8 mmol/L with placebo (P=0.0007).<br><br>Fasting insulin levels decreased more with miglitol compared to placebo, the difference was not significant (P value not reported).<br><br>FPG, fasting and postprandial TG levels showed a descriptive advantage for miglitol, but did not reach a statistical difference. Mean FPG levels fell more with miglitol (baseline, 11.5±2.7 mmol/L; end of treatment, 10.8±3.6 mmol/L) compared to placebo (baseline, 11.6±3.1 mmol/L; end of treatment, 11.5±3.4 mmol/L; difference of adjusted means; P=0.15). Fasting TG levels fell with miglitol (treatment effect, -16.3 mg/dL) compared to placebo (treatment effect, 3.77 mg/dL; P=0.26). Similar results were seen for postprandial TG. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Chiasson et al.[46] (2001)<br><br>Miglitol 100 mg TID<br><br>vs<br><br>metformin 500 mg TID<br><br>vs<br><br>miglitol 100 mg TID plus metformin 500 mg TID<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients >40 years of age with type 2 diabetes inadequately controlled by diet alone, $HbA_{1c}$ 7.2 to 9.5% | N=324<br><br>36 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG, insulin levels, and TG | Primary:<br>Mean change in $HbA_{1c}$ from baseline was 0.38±0.12% with placebo, 0.02±0.10% with miglitol, -0.85±0.12% with metformin, and -1.39±0.11% with combination therapy. A reduction in mean placebo-subtracted $HbA_{1c}$ of -1.78% was seen with combination therapy, and this was significantly different from metformin<br>(-1.25%; P=0.002).<br><br>Mean reductions in $HbA_{1c}$ compared to placebo were -0.37% with miglitol, -1.25% with metformin, and -1.78% with combination therapy. The end of treatment mean $HbA_{1c}$ was 8.5% with placebo, 8.2% with miglitol, 7.3% with metformin, and 6.9% with combination therapy. Significantly more patients (P=0.0014) receiving combination therapy (70.6%) were classified as responders (i.e., showed ≥15% reduction from baseline in $HbA_{1c}$ or achieved an $HbA_{1c}$ <7.0%) compared to metformin (45.5%).<br><br>Secondary:<br>Combination therapy resulted in better metabolic control compared to metformin for FPG (P=0.0025) and two-hour PPG AUC (P=0.0001).<br><br>Changes in TG levels from baseline to trial end did not differ significantly between combination therapy compared to metformin, and showed no consistent trend (P value not reported). |

*Synonym for glyburide.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times a day, TID=three times daily, XL=extended-release
Study abbreviations: AC=active comparator, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SA=single arm, SR=systematic review, XO=crossover
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, DBP=diastolic blood pressure, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide=1, $HbA_{1c}$= glycosylated hemoglobin, HOMA-B=homeostasis model assessment-beta cell function, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HDL-C=high density lipoprotein cholesterol, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, M value=insulin sensitivity, NPP=neutral protamine Hagedorn, PPG=postprandial plasma glucose, RR=risk ratio, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione, $Vo_{2MAX}$=regional fat distribution, WHO=World Health Organization

**Additional Evidence**

Dose Simplification
One small study by Aoki et al. concluded that the effects of alpha-glucosidase inhibitors on glycosylated hemoglobin ($HbA_{1c}$) were similar to those who took it prior to meals (as recommended) and those who took it after meals. Thirty-one type 2 diabetic patients who had never been treated with insulin injections or alpha-glucosidase inhibitors were randomized into two groups. One group took miglitol prior to meals, and the other group took miglitol after meals. After three months, the reduction in $HbA_{1c}$ between the two groups was similar. The authors concluded that for those patients who could not remember to take their alpha-glucosidase inhibitor prior to meals could do so after their meal without a noticeable difference in $HbA_{1c}$.[47]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 9. Relative Cost of the Alpha-Glucosidase Inhibitors**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Acarbose | tablet | Precose®* | $$ | $$ |
| Miglitol | tablet | Glyset® | $$$$-$$$$$ | N/A |

*Generic is available in at least one dosage form or strength.
N/A=Not available

## X. Conclusions

The alpha-glucosidase inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1,2] Acarbose is currently the only agent available in a generic formulation.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin ($HbA_{1c}$) will most likely require combination or triple therapy in order to achieve glycemic goals. At this time,

uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. In general, the α-glucosidase inhibitors are not recommended for use in the management of patients with a high $HbA_{1c}$ (7.6 to 9.0%), mainly due to the limited $HbA_{1c}$-lowering potential associated with the medication class compared to other available antidiabetic medications. The α-glucosidase inhibitors may be utilized as monotherapy in the management of patients with a low $HbA_{1c}$ (6.5 to 7.5%); however, metformin remains the most appropriate initial choice for monotherapy in all patients. In addition, clinical guidelines recognize the potential use of α-glucosidase inhibitors when postprandial hyperglycemia is present. Among all current clinical guidelines, preference of one α-glucosidase inhibitor over another is not stated.[3-12]

A variety of clinical trials have been conducted with the alpha-glucosidase inhibitors. A clinical trial directly comparing acarbose and miglitol does not evaluate glycemic control among type 2 diabetics; rather the results demonstrate that there is no significant difference between the two agents with regards to glucose variability during pre- and post-prandial periods.[31]The majority of the clinical trials have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[19-22,29,30,37,38,40,42,43,44-46] When comparing similar monotherapy treatment regimens, sulfonylureas have been shown to be more effective than the alpha-glucosidase inhibitors.[25,26]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the alpha-glucosidase inhibitors or any other antidiabetic drug.[1,2]

There is insufficient evidence to support that one brand alpha-glucosidase inhibitor is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand alpha-glucosidase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

## XII. References

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Amylinomimetics
# AHFS Class 682003
# November 14, 2012

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service (AHFS) classes, including the alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents that make up these classes differ with regard to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Pramlintide is the only amylinomimetic agent that is currently available. It is approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.[1-3] Amylin is co-secreted with insulin by pancreatic beta cells in response to food intake. It affects postprandial glucose levels by slowing gastric emptying, suppressing glucagon secretion, and regulating food intake via modulation of appetite.[1] Patients with type 1 and type 2 diabetes have dysfunctional beta cells, which leads to a reduced secretion of insulin and amylin in response to food.[1] Pramlintide is a synthetic analog of human amylin, which has been shown to modulate gastric emptying, decrease postprandial glucagon concentrations in patients using insulin, and reduce caloric intake.[1-3]

The amylinomimetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in May 2010.

**Table 1. Amylinomimetics Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Pramlintide | injection | Symlin®, SymlinPen® | none |

PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Amylinomimetics**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[4] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes<br>• An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 1 diabetes<br>• Recommended therapy consists of the following components:<br>  ○ Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy.<br>  ○ Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity.<br>  ○ For many patients, use of insulin analogs.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[5] (2012)** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | therapy.<br><br>Initial drug therapy<br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br>Advancing to dual combination therapy<br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.<br>• Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.<br>• It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.<br>• For all medications, consideration should also be given to overall tolerability.<br><br>Advancing to triple combination therapy<br>• Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.<br>• Many patients, especially those with long standing disease, will |

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>
eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
<ul>
<li>In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.</li>
<li>Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.</li>
</ul>
Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations
<table>
<tr><td>Initial Drug Monotherapy</td><td colspan="5">Metformin</td></tr>
<tr><td>Efficacy (↓$HbA_{1c}$)</td><td colspan="5">High</td></tr>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonyl-urea</td><td>Metformin + thia-zolidinedione (TZD)</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor agonist</td><td>Metformin + insulin (usually basal)</td></tr>
<tr><td>Efficacy (↓$HbA_{1c}$)</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypo-glycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Oedema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td rowspan="2">Three Drug Combin-ations</td><td>Metformin + sulfonyl-urea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td>TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table>
</td></tr>
<tr><td>American College of Physicians (ACCP):<br>Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[6] (2012)</td><td>
<ul>
<li>Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.</li>
<li>Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.</li>
<li>It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.</li>
</ul>
</td></tr>
<tr><td>American Association of Clinical Endocrinologists:</td><td>
<u>Antihyperglycemic pharmacotherapy</u>
<ul>
<li>The choice of therapeutic agents should be based on their differing</li>
</ul>
</td></tr>
</table>

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[7] (2011)** | metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[11]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **Statement by an American Association of Clinical Endocrinologists/American** | <u>Principles underlying the algorithm</u><br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[88] (2009)** | that have complementary mechanisms of action.<br>• Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br><u>Stratification by current $HbA_{1c}$</u><br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br><u>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%</u><br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | its maximally effective dose then triple therapy should be initiated.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + GLP-1 receptor agonist + glinide.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + DPP-4 inhibitor + glinide.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + TZD.<br>  o Metformin + sulfonylurea.<br>  o Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>  o Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>  ○ Metformin + TZD.<br>  ○ Metformin + TZD + sulfonylurea.<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the |

| Clinical Guideline | Recommendation(s) |
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| | increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy.<br><br><u>General Considerations Regarding Insulin Therapy</u><br>• Therapy can be initiated with basal, premixed, prandial, or basal-bolus insulin.<br>• Long-acting basal insulin is generally the initial choice for initiation of insulin therapy. Insulin glargine and insulin detemir are preferred over human NPH insulin because they have relatively peakless time-action curves and a more consistent effect from day to day, resulting in a lower risk of hypoglycemia.<br>• If the patient has failed to achieve goals with the use of basal insulin, an alternative approach would be to use premixed insulin analogs (lispro-protamine or aspart-protamine) with 2 injections per day. The patient must have a fairly constant lifestyle with use of premixed insulin and may have a higher risk of hypoglycemia.<br>• A basal-bolus insulin regimen with four injections per day is usually more efficacious and provides greater flexibility for patients.<br>• Metformin is the most commonly used and safest medication to combine with insulin.<br>• Exenatide and DPP-4 inhibitors have not been approved by the FDA for concomitant use with insulin.<br>• Colesevelam and alpha-glucosidase inhibitors are unlikely to contribute to effectiveness of insulin.<br>• Sulfonylureas and glinides should be discontinued when prandial insulin is started because postprandial glucose can be managed better with a rapid-acting insulin analogue or a premixed insulin preparation.<br>• TZDs in combination with insulin have been associated with weight gain, fluid retention, congestive heart failure, and increased risk of fractures. Recent clinical trials (ADVANCE, VADT, and ACCORD) showed no increased risk of mortality associated with rosiglitazone. The PROACTIVE trial showed a small beneficial effect of pioglitazone on cardiac events. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[9] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>• Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>• Initiate self-monitoring blood glucose levels. |

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| | <u>Glycemic management-patients with type 1 diabetes</u><br>• Initiate intensive insulin therapy with one of the following regimens:<br>  ○ Basal-bolus therapy, using a long-acting insulin analog in combination with a rapid-acting insulin analog or inhaled insulin at meals.<br>  ○ Continuous SC insulin infusion with an insulin pump; insulin pump therapy indicated for:<br>  ▪ Patients unable to achieve control using a regimen of multiple daily injections.<br>  ▪ Patients with histories of frequent hypoglycemia and/or hypoglycemia unawareness.<br>  ▪ Patients who are pregnant.<br>  ▪ Patients with extreme insulin sensitivity (pump therapy facilitates better precision than SC injections).<br>  ▪ Patients with a history of dawn phenomenon (these patients can program a higher basal rate for the early morning hours to counteract the rise in blood glucose concentration).<br>  ▪ Patients who require more intensive diabetes management because of complications including neuropathy, nephropathy, and retinopathy.<br>  ▪ Patients taking multiple daily injections who have demonstrated willingness and ability to comply with prescribed diabetes self-care behavior including frequent glucose monitoring, carbohydrate counting, and insulin adjustment.<br>• Consider adding pramlintide to intensive insulin therapy to enhance glycemic control and to assist with weight management.<br>• Consider adding an insulin sensitizer to address insulin resistance as needed. Exercise caution because of the potential for increased fluid retention when TZDs are used with insulin.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>  ○ First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. |

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| | ○ After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>○ If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>○ Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>○ Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>○ Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>○ Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 1 diabetes</u><br>• Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose |

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| | levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range.<br>• Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated.<br>• Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients.<br>• Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability.<br>• Carefully assess PPG levels when the $HbA_{1c}$ level is elevated and pre-meal glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable $HbA_{1c}$ level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia.<br>• Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs.<br>• Individualize insulin regimens to accommodate patient exercise patterns.<br>• Treat hypoglycemic reactions with simple carbohydrates.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer** | <u>4 inhibitors</u><br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is |

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| **Agents[10] (2009)** | inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in 6 months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br><u>TZDs</u><br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  o A body mass index ≥35 $kg/m^2$ in those of European descent (with appropriate adjustment for other ethnic groups).<br>  o A BMI <35 $kg/m^2$, and therapy with insulin would have |

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| | significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  o A person prefers injecting insulin immediately before a meal.<br>  o Hypoglycemia is a problem.<br>  o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>  o Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>  o Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>  o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>  o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>  o Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[11] (2008)** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br><u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is |

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| | required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>  o The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>  o A sulfonylurea if metformin is not tolerated.<br>  o Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br><u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u><br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/m$^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  o Inadequate blood glucose control ($HbA_{1c}$ ≥7.5%) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  o Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started.<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  o Continue with metformin and the sulfonylurea (and acarbose, |

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| | if used).<br>○ Review the use of the sulfonylurea if hypoglycemia occurs.<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>○ Continue with metformin.<br>○ Continue the sulfonylurea initially and discontinue if hypoglycemia occurs.<br>• Consider combining pioglitazone with insulin therapy for:<br>○ Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>○ Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>○ Those who require assistance from a care taker or healthcare professional to administer their insulin injections.<br>○ Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes.<br>○ Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ >9.0 %. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>○ Immediate injection before a meal is preferred.<br>○ Hypoglycemia is a problem.<br>○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI):<br>**Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[12] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |

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| | Insulin as an adjunct to oral therapy<br>• A once-daily dose of NPH, detemir or glargine insulin is added to metformin or TZDs. If patient is also on a sulfonylurea, it may be discontinued or reduced when insulin is added.<br>• A once-daily dose of insulin is added to sulfonylurea. Glargine or detemir may be dosed in the morning or evening. Morning dosing may prevent nighttime hypoglycemic episodes and may also provide for improved blood glucose control.<br><br>Insulin alone<br>• Twice-daily insulin regimen is established with progression to increased frequency of insulin administration as necessary to achieve treatment goals or to add flexibility to a patient's meal and activity schedules.<br>• Multiple dose insulin with rapid-acting and basal insulin therapy may offer patients with active lifestyles the greatest flexibility.<br><br>Oral agents as an adjunct to insulin therapy<br>• Metformin may be a useful adjunct for patients who require large doses of insulin (>100 units/day). |
| International Diabetes Federation (IDF) Clinical Guidelines Task Force:<br>**Global Guideline for Type 2 Diabetes[13] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br>Insulin<br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |
| American Diabetes Association (ADA):<br>**Care of Children and Adolescents with Type 1 Diabetes[14] (2005)** | • Insulin type, mixture of insulins, site of injection, and individual patient response differences can all affect the onset, peak, and duration of insulin activity.<br>• Children with diabetes often require multiple daily injections of insulin, using combinations of rapid-, short-, intermediate-, or long-acting insulin before meals and at bedtime to maintain optimal blood glucose control.<br>• The basal/bolus insulin regimen uses a long-acting insulin analog |

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| | combined with a rapid-acting insulin analog given before meals and snacks. This regimen has been shown to result in stable glycemic control and less hypoglycemia compared with regimens using intermediate and short insulin regimens.<br>• Many young children and teenagers consume multiple snacks throughout the day. An ideal basal/bolus regimen may consist of as many as six to seven insulin injections per day. A combination of rapid-acting insulin with small amounts of intermediate-acting insulin to allow coverage for snacks may be an appropriate alternative to the basal/bolus plan. However, two or three doses of mixed rapid-acting or short-acting insulin with intermediate-acting insulin generally cannot maintain $HbA_{1c}$ levels within the target range. Recommendations now support moving toward a basal/bolus insulin regimen for most patients.<br>• The combination of rapid-acting insulin analogs and a long-acting insulin offers an excellent option for basal and bolus insulin administration.<br>• Basal/bolus regimens have been shown to result in lower fasting blood glucose levels with less nocturnal hypoglycemia than regimens that use NPH insulin in children/adolescents, as well as in adults. |
| National Institute for Clinical Excellence (NICE): **Managing Type 1 Diabetes in Adults (full guideline part 2)[15] (2008)** | Insulin regimens<br>• Patients should have access to the types (preparation and species) of insulin they find allow them optimal well-being.<br>• Cultural preferences need to be discussed and respected in agreeing on the insulin regimen for a patient.<br>• Multiple insulin injection regimens, in patients who prefer them, should be used as part of an integrated package of which education, food, and skills training should be integral parts.<br>• Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes.<br>• Mealtime insulin injections should be provided by injection unmodified ('soluble') insulin or rapid-acting insulin analogs before main meals.<br>• Rapid-acting insulin analogs should be used as an alternative to mealtime unmodified insulin where nocturnal or late inter-prandial hypoglycemia is a problem, and in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired.<br>• Basal insulin therapy (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogs (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogs are given at mealtimes or the midday insulin dose is small or lacking, the need to give isophane (NPH) insulin twice-daily (or more often) should be considered.<br>• Long-acting insulin analogs (insulin glargine) should be used when:<br>  ○ Nocturnal hypoglycemia is a problem on isophane (NPH) insulin.<br>  ○ Morning hypoglycemia on isophane (NPH) insulin results in difficult daytime blood glucose control.<br>  ○ Rapid-acting insulin analogues are used for mealtime blood glucose control.<br>• Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life:<br>  ○ Biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance. |

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| | ○ Biphasic rapid-acting insulin analog pre-mixes may give an advantage to those prone to hypoglycemia at night.<br>○ Such twice-daily regimens may also help:<br>▪ Those who find adherence to their agreed lunchtime insulin injection difficult.<br>▪ Those with learning difficulties who may require assistance from others.<br>• Patients whose nutritional and physical activity patterns vary considerably from day-to-day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations and consideration of unusual patterns and combinations.<br>• For patients undergoing periods of fasting or sleep following eating (e.g., during religious feasts and fasts, after night-shift work), a rapid-acting insulin analog before the meal (provided the meal is not prolonged) should be considered.<br>• For patient with erratic and unpredictable blood glucose control, rather than a change in a previously optimized insulin regimen, the following should be considered:<br>○ Re-suspension of insulin and injection technique.<br>○ Injection sites.<br>○ Self-monitoring skills.<br>○ Knowledge and self-management skills.<br>○ Nature of lifestyle.<br>○ Psychological and psychosocial difficulties.<br>○ Possible organic causes (e.g., gastroparesis).<br>• Continuous SC insulin infusion is recommended as an option provided that:<br>○ Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and<br>○ Patients receiving the treatment have the commitment and competence to use the therapy effectively.<br>• Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some mealtime insulin) should be considered for patients initiating insulin therapy, until such time as islet β-cell deficiency progresses further.<br>• Clear guidelines and protocols should be given to all patients to assist them in adjusting insulin doses appropriate during intercurrent illness.<br>• Oral glucose-lowering drugs should generally not be used in the management of type 1 diabetics.<br><br><u>Insulin delivery</u><br>• Patients who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen.<br>• Patients who have special visual or psychological needs should be provided with injection devices or needle-free systems that they can use independently for accurate dosing.<br>• Insulin injection should be made into the deep SC fat. To achieve this, needles of a length appropriate to the individual should be made available.<br>• Patients should be informed that the abdominal wall is the therapeutic choice for mealtime insulin injections.<br>• Patients should be informed that extended-acting suspension insulin (e.g., isophane [NPH] insulin) may give a longer profile of action when |

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| | injected into the SC tissue of the thigh rather than the arm or abdominal wall.<br>• Patients should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within that area.<br>• Patients should be provided with suitable containers for the collection of used needles. Arrangements should be available for the suitable disposal of these containers.<br>• Injection site condition should be checked annually, and if new problems with blood glucose control occur. |
| National Institute for Clinical Excellence (NICE)/National Collaborating Center for Women's and Children's Health: **Diagnosis and Management of Type 1 Diabetes in Children and Young People[16] (2004 and 2009 Update)** | <u>Insulin regimens</u><br>• Pre-school and primary school children should be offered the most appropriate individualized regimens to optimize glycemic control.<br>• Young people should be offered multiple daily injection regimens to help optimize glycemia control.<br>• As it improves glycemic control, multiple daily injection regimens should be offered only as part of a package of care that involves continuing education; dietary management; instruction on the use of insulin delivery systems and blood glucose monitoring; emotional and behavioral support; and medical, nursing, and dietetic expertise in pediatric diabetes.<br>• Children and young people using multiple daily injection regimens should be informed that they may experience an initial increase in the risk of hypoglycemia and short-term weight gain.<br>• Children and young people and their families should be informed about strategies for the avoidance and management of hypoglycemia.<br>• Young people who do not achieve satisfactory glycemic control with multiple daily injection regimens should be offered additional support and, if appropriate, alternative insulin therapy (once, twice, or three times daily mixed insulin regimens or continuous SC insulin infusion using an insulin pump).<br>• Young people who have difficulty adhering to the multiple daily injection regimens should be offered twice-daily injection regimens.<br>• Continuous SC insulin infusion is recommended as an option for patients provided that:<br>  ○ Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and;<br>  ○ Patients receiving the treatment have the commitment and competence to use the therapy effectively.<br>• Continuous SC insulin infusion therapy should be initiated only by a trained specialist team.<br>• All individuals beginning continuous SC insulin infusion therapy should be provided with specific training in its use.<br>• Established users of continuous SC insulin infusion therapy should have their insulin management reviewed by their specialist team so that a decision can be made about whether a trial or a switch to multiple-dose insulin incorporating insulin glargine would be appropriate.<br><br><u>Insulin preparations</u><br>• Children and young people should be offered the most appropriate insulin preparations according to their individual needs with the aim of obtaining an $HbA_{1c}$ <7.5% without frequent disabling hypoglycemia and maximizing quality of life.<br>• Children and young people using multiple daily insulin regimens should be informed that injection of rapid-acting insulin analogs before |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | eating (rather than after eating) reduces PPG levels thus helps to optimize blood glucose control.<br>• For pre-school children it may be appropriate to use rapid-acting insulin analogs shortly after eating (rather than before eating) because food intake can be unpredictable.<br>• Children and young people who use insulin preparations containing intermediate-acting insulin should be informed that these preparations should be mixed before use according to instructions provided in patient information leaflets.<br><br><u>Insulin delivery</u><br>• Children and young people should be offered a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences.<br>• Children and young people using insulin injection regimens should be offered needles that are of an appropriate length for their body fat.<br><br><u>Non-insulin agents (oral antidiabetic agents)</u><br>• Children and young people should not be offered acarbose or sulfonylureas in combination with insulin because they may increase the risk of hypoglycemia without improving glycemic control.<br>  ○ Metformin in combination with insulin is suitable for use only within research trials because the effectiveness of this combination therapy in providing glycemic control is uncertain. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the amylinomimetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Amylinomimetics[1]**

| Indication | Pramlintide |
|---|---|
| Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy | ✔ |
| Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin | ✔ |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the amylinomimetics are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the Amylinomimetics[1-3]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Half-Life (hours) |
|---|---|---|---|---|
| Pramlintide | 30 to 40 | Not extensively protein bound | Renal | 0.50 to 0.83 |

## V. Drug Interactions

There are no significant drug interactions reported with the amylinomimetics.[1-3] Due to its effects on gastric emptying, pramlintide should not be considered for patients taking drugs that alter gastrointestinal motility (e.g., anticholinergic agents) and agents that slow the intestinal absorption of nutrients (e.g., alpha-glucosidase inhibitors).[1] Pramlintide has the potential to delay the absorption of concomitantly administered oral medications. When the rapid onset of a concomitant administered oral agent is a critical determinant of effectiveness, the agent should be administered at least one hour prior to or two hours after pramlintide injection.[1]

## VI. Adverse Drug Events

The most common adverse drug events reported with the amylinomimetics are listed in Table 5. The boxed warning for pramlintide is listed in Table 6. When used alone, pramlintide does not cause hypoglycemia; however, when co-administered with insulin, there is an increased risk of insulin-induced severe hypoglycemia. Severe hypoglycemia occurs within the first three hours following administration of pramlintide.

**Table 5. Adverse Drug Events (%) Reported with the Amylinomimetics[1-3]**

| Adverse Event | Pramlintide* |
|---|---|
| **Central Nervous System** | |
| Dizziness | 2 to 6 |
| Fatigue | 3 to 7 |
| Headache | 5 to 13 |
| **Gastrointestinal** | |
| Abdominal pain | 2 to 8 |
| Anorexia | 0 to 17 |
| Nausea | 28 to 48 |
| Vomiting | 7 to 11 |
| **Respiratory** | |
| Coughing | 2 to 6 |
| Pharyngitis | 3 to 5 |
| **Other** | |
| Allergic reaction | <1 to 6 |
| Arthralgia | 2 to 7 |
| Inflicted injury | 8 to 14 |
| Severe hypoglycemia (medically assisted) | 0.4 to 7.3 |
| Severe hypoglycemia (patient-ascertained) | 0.6 to 16.8 |

*In combination with insulin therapy.

**Table 6. Boxed Warning for the Amylinomimetics[1-3]**

| WARNING |
|---|
| Pramlintide is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with pramlintide use occurs, it is seen within 3 hours following a pramlintide injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk. |

## VII. Dosing and Administration

The usual dosing regimens for the amylinomimetics are listed in Table 7.

**Table 7. Usual Dosing Regimens for the Amylinomimetics[1-3]**

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| Pramlintide | Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy:<br>Multi-dose pen, vial: initial, 15 µg SC immediately prior to major meals; maintenance, 30 to 60 µg SC immediately prior to major meals<br><br>Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin:<br>Multi-dose pen, vial: initial, 60 µg SC immediately prior to major meals; maintenance, 60 to 120 µg SC immediately prior to major meals | Safety and efficacy in children have not been established. | Multi-dose Pen:<br>1,000 µg/mL*<br><br>Vial:<br>600 µg/mL (5 mL) |

SC=subcutaneous

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the amylinomimetics are summarized in Table 8.

**Table 8. Comparative Clinical Trials with the Amylinomimetics**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Type 1 Diabetes** | | | | |
| Edelman et al.[17] (2006)<br><br>Pramlintide 15 to 60 µg with meals and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen) | DB, MC, PC, RCT<br><br>Type 1 diabetic patients <18 years of age with an $HbA_{1c}$ 7.5 to 9.0%, intensely or continuously treated with insulin for the past year, and with no severe hypoglycemic event over the preceding 6 months | N=296<br><br>29 weeks | Primary:<br>Safety<br><br>Secondary:<br>Change from baseline in $HbA_{1c}$, PPG concentrations, insulin, and weight; tolerability | Primary:<br>Both treatments resulted in a similar number of nonsevere hypoglycemic events. The event rate per patient years was 0.57 with pramlintide compared to 0.30 with placebo (P<0.05).<br><br>Secondary:<br>Baseline $HbA_{1c}$ was 8.1% with both treatments and at week 29 had decreased comparably (-0.50; 95% CI, -0.61 to -0.33 vs -0.50%; 95% CI, -0.63 to -0.35; P value not reported).<br><br>Among pramlintide-treated patients, a significantly greater number were able to achieve a PPG concentration of 9.9 mmol/L at breakfast (68 vs 51%), lunch (71 vs 61%), and dinner (70 vs 58%; P<0.0001 for each meal).<br><br>At week 29 the total insulin dose with pramlintide decreased by -12% compared to an increase of 1% with placebo.<br><br>Between weeks 0 through 29, the reduction in body weight was significant with pramlintide compared to placebo (-1.3 vs 1.2 kg; P<0.0001).<br><br>Reduced appetite, vomiting, and sinusitis occurred at twice the level with pramlintide compared to placebo (P<0.01). |
| Whitehouse et al.[18] (2002)<br><br>Pramlintide 30 to 60 µg QID and insulin (existing regimen) | DB, PC, RCT<br><br>Type 1 diabetic patients | N=480<br><br>52 weeks | Primary:<br>Change from baseline $HbA_{1c}$<br><br>Secondary:<br>Change from baseline $HbA_{1c}$ and body weight at | Primary:<br>Significantly greater reductions in $HbA_{1c}$ were observed with pramlintide (-0.39%) compared to placebo (-0.12%; P=0.0071) at 52 weeks.<br><br>Secondary:<br>Significantly greater reductions in $HbA_{1c}$ with pramlintide were achieved at weeks 13 (-0.67 vs -0.16%; P<0.0001), 26 (-0.58 vs -0.18%; P=0.0001), and 52 (-0.39 vs -0.12%; P=0.0071). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>placebo and insulin (existing regimen) | | | weeks 13, 26, and 52 | Pramlintide-treated patients had sustained reductions in body weight that were significantly different compared to placebo-treated patients (P<0.001) from week 13 onward (data reported in graphical form only).<br><br>The most commonly reported side effects with pramlintide were nausea (46.5 vs 21.9%; P values not reported) and anorexia (17.7 vs 2.1%; P values not reported). Withdrawal due to adverse event(s) occurred in 31 (12.8%) and 19 (8.0%) pramlintide- and placebo-treated patients. |
| Ratner et al.[19] (2004)<br><br>Pramlintide 60 µg TID, 60 µg QID, or 90 µg TID and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen) | DB, PC, RCT<br><br>Type 1 diabetics | N=651<br><br>52 weeks | Primary:<br>Change from baseline $HbA_{1c}$ at week 26<br><br>Secondary:<br>Change from baseline $HbA_{1c}$ at week 52, proportion of patients achieving $HbA_{1c}$ <7.0%, safety | Primary:<br>Significantly greater reductions in $HbA_{1c}$ were achieved with pramlintide 60 µg TID compared to placebo (-0.41 vs -0.18%; P=0.012) after 26 weeks. In addition, significantly greater reductions in $HbA_{1c}$ were achieved with pramlintide 60 µg QID compared to placebo (-0.39 vs -0.18%; P=0.013).<br><br>Secondary:<br>Significantly greater reductions in $HbA_{1c}$ were achieved with pramlintide 60 µg TID compared to placebo (-0.29 vs -0.04%; P=0.011) after 52 weeks. In addition, significantly greater reductions in $HbA_{1c}$ were achieved with pramlintide 60 µg QID compared to placebo (-0.34 vs -0.04%; P=0.001).<br><br>A threefold greater proportion of pramlintide-treated patients achieved $HbA_{1c}$ <7.0% compared to placebo treated patients (P value not reported; data was reported in graphical form only). Pramlintide 90 µg was excluded from the analysis when results from a separate trial indicated the dose had an adverse tolerability profile. Patients originally randomized to this treatment continued to receive 90 µg to preserve the trial design.<br><br>During the first four weeks of therapy, pramlintide-treated patients had a fourfold increase in severe hypoglycemic event rate compared to placebo-treated subjects (3.78 vs 0.87 events/year; no P value reported). The most commonly reported adverse event with pramlintide was nausea. Withdrawal due to adverse event(s) occurred in 38 (22.1%) patients receiving pramlintide 90 µg TID, 22 (13.7%) patients receiving pramlintide 60 µg QID, 32 (19.5%) patients receiving pramlintide 60 µg |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | TID, and six (3.9%) patients receiving placebo. |
| Marrero et al.[20] (2007)<br><br>Pramlintide 15 to 60 µg with meals and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen) | Post hoc analysis<br><br>Type 1 diabetic patients who completed a 29 week DB, noninferiority, dose-finding pramlintide trial | N=266<br><br>29 weeks | Primary:<br>Patient response to satisfaction questionnaire<br><br>Secondary:<br>Not reported | Primary:<br>For the following topics the survey ratings favored pramlintide: Study medication (1) "made my blood glucose control more even or predictable," (2) "provided me with more flexibility in what I can eat," (3) "made it easier to control my weight," and (4) "made it easier to control my appetite" (P<0.05 for all).<br><br>There was no difference between treatments in the response to the following statements: Study medication (1) "made it easier to avoid low blood sugar reactions (hypoglycemia)" and (2) "I would like to continue taking the study medication" (P value not significant).<br><br>Secondary:<br>Not reported |
| Ratner et al.[21] (2005)<br><br>Pramlintide and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen) | MA (3 trials)<br><br>Type 1 diabetic patients with $HbA_{1c}$ 7.0 to 8.5% | N=477<br><br>26 weeks | Primary:<br>Change from baseline in $HbA_{1c}$ and body weight, adverse events (hypoglycemia)<br><br>Secondary:<br>Not reported | Primary:<br>Significant baseline reductions in $HbA_{1c}$ (-0.3%) and body weight (-1.8 kg) at endpoint were achieved with pramlintide (P<0.0009 for both).<br><br>The risk of severe hypoglycemia was 1.40 with pramlintide compared to 1.86 with placebo.<br><br>Secondary:<br>Not reported |
| Heptulla et al.[22] (2009)<br><br>Pramlintide 3 to 5 µg /hour as a basal dose and insulin infusion (existing regimen was reduced by 30%) | RCT<br><br>Adolescents with type 1 diabetes mellitus on insulin pump therapy | N=13<br><br>24 hours | Primary:<br>PPG, glucagon, and insulin concentrations<br><br>Secondary:<br>Not reported | Primary:<br>Postprandial hyperglycemia was reduced by 26% with pramlintide compared to placebo (P<0.008).<br><br>Postprandial glucagon concentrations were suppressed with pramlintide compared to placebo (P<0.003).<br><br>The plasma insulin concentrations were unchanged.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>insulin infusion (existing regimen) | | | | Not reported |
| **Type 2 Diabetes** | | | | |
| Singh-Franco et al.[23] (2011)<br><br>Pramlintide 120 to 150 µg SC BID or TID with meals | MA (8 trials)<br><br>Type 2 diabetic patients (4 trials) and obese patients without diabetes (4 trials) | N=1,616<br><br>6 to 52 weeks | Primary:<br>Change from baseline in $HbA_{1c}$<br><br>Secondary:<br>Likelihood of achieving $HbA_{1c}$ ≤7.0%; change from baseline in FPG, PPG, and weight | Primary:<br>Pooled analysis revealed that compared to placebo, pramlintide was associated with a baseline reduction in $HbA_{1c}$ of -0.33% (P=0.0004).<br><br>Secondary:<br>After 52 weeks, pramlintide-treated patients were 1.52 times (95% CI, 0.83 to 2.78) more likely to achieve an $HbA_{1c}$ ≤7.0% compared to placebo treated patients; however, this difference was not significant (P=0.18).<br><br>Treatment with pramlintide was associated with a reduction from baseline in FPG of -6.34 mg/dL (95% CI, -24.96 to 12.28) over 24 weeks of treatment, but the difference was not significant (P=0.50).<br><br>Treatment with pramlintide was associated with a reduction from baseline in PPG of -7.20 mg/dL (95% CI, -40.12 to 25.75) over 24 weeks of treatment, but the difference was not significant (P=0.67).<br><br>Pramlintide was associated with a significant change in body weight in patients with type 2 diabetes compared to placebo (-2.21 kg; P<0.000001). |
| Karl et al.[24] (2007)<br><br>Pramlintide 120 µg before meals and insulin (existing regimen) | MC, OL<br><br>Type 2 diabetics >18 years of age currently receiving insulin therapy with or without oral antidiabetics, and $HbA_{1c}$ >7.0 to <11.0% | N=166<br><br>12 months (all results reported at 6 months) | Primary:<br>Change from baseline in $HbA_{1c}$, FPG, PPG, body weight, and insulin; safety<br><br>Secondary:<br>Not reported | Primary:<br>Pramlintide resulted in significant $HbA_{1c}$ reductions at months three and six (-0.66 and -0.56%; P<0.05). At some point during the initial six months after initiating therapy, 28.1% of the patients who had a baseline $HbA_{1c}$ >7.0% achieved an $HbA_{1c}$ <7.0%.<br><br>Compared to baseline, both fasting and PPG concentrations were significantly reduced (P<0.05).<br><br>Significant baseline reductions in weight were noted at months three and six (-2.3 and -2.8 kg; P<0.05).<br><br>At months three and six, mealtime and total insulin doses remained |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | significantly lower compared to baseline (P<0.05).<br><br>Nausea (29.5%), vomiting (7.2%), and diarrhea (5.4%) were the most commonly reported adverse events. There was an overall incidence of 12% for hypoglycemia, with two patients experiencing severe hypoglycemia during the six month treatment period.<br><br>Secondary:<br>Not reported |
| Riddle et al.[25] (2007)<br><br>Pramlintide 60 µg SC BID or TID with meals, titrated to 120 µg SC<br><br>vs<br><br>placebo<br><br>All patients also received existing insulin regimens. | DB, MC, PC, RCT<br><br>Type 2 diabetics 25 to 75 years of age not achieving adequate glycemic control with insulin glargine (no mealtime insulin), with or without oral antidiabetic therapy, and an $HbA_{1c}$ >7.0 to 10.5% and BMI 25 to 45 kg/m$^2$ | N=212<br><br>16 weeks | Primary:<br>Change from baseline $HbA_{1c}$ at week 16, proportion of patients meeting all of the following prespecified criteria at week 16: $HbA_{1c}$ ≤7.0% or an $HbA_{1c}$ baseline reduction ≥0.5%, mean daily PPG increments ≤40 mg/dL, no weight gain, and no severe hypoglycemia<br><br>Secondary:<br>Individual components of the composite endpoint; proportion of patients achieving $HbA_{1c}$ ≤7.0 or | Primary:<br>Pramlintide-treated patients experienced significantly greater baseline reductions in $HbA_{1c}$ at week 16 compared to placebo –treated patients (-0.70 vs -0.36%; P<0.05).<br><br>At week 16, significantly more pramlintide-treated patients achieved the composite endpoint compared to placebo-treated patients (25 vs 7%; P<0.001).<br><br>Secondary:<br>The proportion of patients who achieved an $HbA_{1c}$ ≤7.0% or who had a reduction in $HbA_{1c}$ ≥0.5% was not different between pramlintide and placebo (54 vs 45%; P value not reported).<br><br>Significantly more pramlintide-treated patients achieved mean PPG increments ≤40 mg/dL (P<0.0001) and did not experience weight gain (P<0.0001) compared to placebo-treated patients.<br><br>Compared to placebo-treated patients, more pramlintide-treated patients achieved both $HbA_{1c}$ and PPG components (P<0.005), more patients reached the $HbA_{1c}$ goal without weight gain (P<0.0001), and more patients had well controlled PPG without weight gain (P<0.0001).<br><br>The proportion of patients achieving an $HbA_{1c}$ ≤7.0 or ≤6.5% was 23 and 11% with pramlintide compared to 13 and 4% with placebo, respectively (P values not reported).<br><br>The insulin glargine dosage increased steadily throughout the trial. The |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | ≤6.5%; changes from baseline to each time point in $HbA_{1c}$, seven-point glucose profiles, PPG increments, FPG, weight, and insulin glargine dose | mean increase in insulin glargine dosage at week 16 was 11.7±1.9 and 13.1±1.6 units with pramlintide and placebo, respectively (P value not reported).<br><br>The average change from baseline in FPG was -28.3 and -12.0 mg/dL at week 16 with pramlintide and placebo, respectively (P value not reported).<br><br>At week 16, PPG was significantly decreased from baseline with pramlintide compared to placebo (-24.4 vs -0.4 mg/dL; P<0.0001).<br><br>By week 16, pramlintide was associated with weight loss compared to weight gain with placebo (-1.6 vs 0.7 kg; P<0.0001) By the end of treatment, 68% of pramlintide-treated patients had lost weight compared to approximately 35% of placebo-treated patients (P<0.0001). |
| Hollander et al.[26] (2003)<br><br>Pramlintide 60, 90, or 120 µg SC BID and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen)<br><br>Data for patients randomized to pramlintide 60 µg SC BID are not reported. | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics >18 years of age requiring insulin therapy for ≥ 6 months prior to trial initiation with an $HbA_{1c}$ ≥8.0%, and without hypoglycemia in the 2 weeks preceding the trial | N=656<br><br>12 months | Primary:<br>Change from baseline in $HbA_{1c}$ at week 26<br><br>Secondary:<br>Absolute change in $HbA_{1c}$ at other time points, proportion of patients who achieved an $HbA_{1c}$ <7.0 or <8.0% | Primary:<br>After 26 weeks, pramlintide 120 µg was associated with a significant reduction in $HbA_{1c}$ compared to placebo (-0.68; P<0.05), but no difference in the baseline reduction of $HbA_{1c}$ was reported between the pramlintide 90 µg and placebo (-0.54%; P value not reported).<br><br>Secondary:<br>After 52 weeks, pramlintide 120 µg was associated with a significant baseline reduction in $HbA_{1c}$ compared to placebo (-0.62; P<0.05), but no difference in the baseline reduction of $HbA_{1c}$ was reported between pramlintide 90 µg and placebo (-0.35%; P value not reported).<br><br>More patients receiving pramlintide (either dose) achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (9.4 and 12.2 vs 4.1%, respectively; P value not reported). Similarly, 42.4, 45.7, and 27.6% of patients receiving pramlintide 90 µg, pramlintide 120 µg, and placebo, respectively, achieved an $HbA_{1c}$ <8.0% (P value not reported). |
| Ratner et al.[27] (2002)<br><br>Pramlintide 30 to | DB, PC, RCT<br><br>Type 2 diabetic patients | N=538<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$ and body weight at weeks | Primary:<br>Significantly greater reductions in $HbA_{1c}$ were achieved with pramlintide 75 µg compared to placebo (-0.9%; *P*=0.0004) after 13 weeks. In addition, $HbA_{1c}$ was significantly lower for the majority of the study periods with |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| 150 µg TID and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen) | | | 13, 26, and 52<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ <7.0 or 8.0%, relative change of insulin use, safety | the exception of week 52 (*P* value not reported).<br><br>Significantly greater reductions in $HbA_{1c}$ were achieved with pramlintide 150 µg compared to placebo (-1.0%; *P*=0.0002). After 13 weeks, $HbA_{1c}$ remained significantly lower for the rest of the trial (-0.6%; *P*=0.0068).<br><br>Reductions in $HbA_{1c}$ with pramlintide 30 µg were not different compared to placebo at any point during the trial.<br><br>Significant baseline reductions (*P*<0.05) in body weight were achieved with all pramlintide doses throughout the trial when compared to placebo.<br><br>Secondary:<br>The proportions of patients achieving an $HbA_{1c}$ <7.0% were 12.7, 13.4, and 19.2% in patients receiving pramlintide 30, 75, and 150 µg compared to 11.1% in patients receiving placebo (*P* values not reported).<br><br>The proportions of patients achieving an $HbA_{1c}$ <8.0% were 45.1, 46.4, and 54.0% in patients receiving pramlintide 30, 75, and 150 µg compared to 37.6% in patients receiving placebo (*P* values not reported).<br><br>Insulin use increased with all treatments. With pramlintide, insulin use increased by 7.9 to 10.9%, while insulin use increased by 15.4% with placebo (*P* values not reported).<br><br>The most commonly reported side effect with pramlintide was nausea. |
| Hollander et al.[28] (2003)<br><br>Pramlintide 120 µg BID and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing | Post hoc analysis<br><br>Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT | N=186<br><br>26 and 52 weeks | Primary:<br>Change in baseline $HbA_{1c}$, body weight, insulin use, and the rate of severe hypoglycemia at week 26; safety<br><br>Secondary:<br>Not reported | Primary:<br>At week 26, the difference in $HbA_{1c}$ baseline reduction with pramlintide compared to placebo was- 0.43% (P<0.0009). The proportion of patients who achieved an $HbA_{1c}$ <7.0% at week 26 was 14% in the pramlintide group compared to 2% in the placebo group (P value was not reported).<br><br>At week 26, the difference in weight baseline reduction with pramlintide compared to placebo was 2 kg (P<0.0003).<br><br>No significant change in insulin dose or the number of insulin injections was noted between the treatments (P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| regimen) | | | | At week 26, no significant difference was noted between the treatments in rates of severe hypoglycemia as reported in event rate per subject year (0.13 vs 0.19; P value not reported).<br><br>No serious adverse events were reported with either treatment.<br><br>Secondary:<br>Not reported |
| Maggs et al.[29] (2003)<br><br>Pramlintide 120 µg BID or pramlintide 150 µg TID and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen) | Post hoc analysis<br><br>Type 2 diabetic patients who completed a 52 week, DB, PC, RCT | N=410<br><br>52 weeks | Primary:<br>Change in baseline in $HbA_{1c}$ and weight at week 52, safety<br><br>Secondary:<br>Not reported | Primary:<br>A significantly greater baseline reduction in $HbA_{1c}$ was achieved with pramlintide compared to placebo at week 52 (P<0.0001). This result was seen across the following ethnic groups: African Americans (-0.7%), Caucasians (-0.5%), and Hispanics (-0.3%).<br><br>A significant baseline reduction in body weight was achieved with pramlintide compared to placebo at week 52 (-2.6 kg; P<0.0001).<br><br>Nausea was more common with pramlintide, and hypoglycemia was reported to a similar extent with both treatments.<br><br>Secondary:<br>Not reported |
| Hollander et al.[30] (2004)<br><br>Pramlintide 120 µg BID and insulin (existing regimen)<br><br>vs<br><br>placebo and insulin (existing regimen) | Post hoc analysis<br><br>Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT | N=498<br><br>26 and 52 weeks | Primary:<br>Change in baseline $HbA_{1c}$, insulin dose, and body weight<br><br>Secondary:<br>Not reported | Primary:<br>At week 26, mean baseline reductions in $HbA_{1c}$ with pramlintide compared to placebo (-0.59 vs -0.18%; P<0.0001).<br><br>There was no difference in the change in total daily insulin requirements between the two treatments.<br><br>At week 26, pramlintide-treated patients achieved a significant baseline reduction in weight compared to placebo (-1.5 vs 0.3 kg; P<0.0001).<br><br>Secondary:<br>Not reported |
| Riddle et al.[31] (2009) | MC, OL | N=113 | Primary:<br>Proportion of | Primary:<br>Thirty percent of pramlintide-treated patients achieved an $HbA_{1c} \leq 7\%$ |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Pramlintide 120 µg prior to meals and basal insulin (QD to BID)<br><br>vs<br><br>rapid-acting insulin analogs 5 units before meals (titrated) and basal insulin (QD to BID) | Type 2 diabetic patients who were inadequately controlled using basal insulin and prior oral antihyperglycemic agents | 24 weeks | patients achieving an $HbA_{1c}$ ≤7.0%<br><br>Secondary: Individual components of the composite end point, insulin dose, $HbA_{1c}$, change in $HbA_{1c}$, proportion of patients reaching $HbA_{1c}$ ≤6.5%, FPG, PPG increments, changes in weight, changes in waist circumference, and adverse events including the incidence, severity, and time courses of hypoglycemia and nausea | compared to 11% of the patients receiving rapid-acting insulin analogs (P=0.018) with a similar dose of basal insulin.<br><br>Secondary:<br>Mean $HbA_{1c}$ at 24 weeks was 7.2% with addition of pramlintide and 7.0% with addition of a rapid acting insulin analog. The least squares mean reduction of $HbA_{1c}$ from baseline was -1.1% for pramlintide and -1.3% for rapid acting insulin analogs (P=0.46 between groups).<br><br>$HbA_{1c}$ ≤6.5% at 24 weeks was achieved by 29% of patients treated with pramlintide and by 34% of patients treated with a rapid-acting insulin analog (P=0.68 between groups).<br><br>At week 24, mean weights were 106 kg (pramlintide) versus 109 kg (rapid-acting insulin analog). Least squares mean changes in weight from baseline were 0.0kg (pramlintide) versus 4.7 kg (rapid-acting insulin analog; P<0.0001).<br><br>Differences in waist measurements were consistent with weight differences. Waist circumferences at week 24 were 115 cm and 120 cm for the pramlintide and rapid-acting insulin analog groups, respectively. Least squares mean changes in waist circumference from baseline were -0.6 cm and 2.2 cm, respectively (P=0.016)<br><br>Similar basal insulin titration in both treatment arms resulted in similar mean FPG concentrations at week 24: 122 mg/dl (pramlintide) and 123 mg/dl (rapid-acting insulin analog) The least squares mean change of FPG from baseline was -31 mg/dl (pramlintide) and -34 mg/dl (rapid-acting insulin analog; P=0.65).<br><br>An FPG concentration <100 mg/dl was achieved at week 24 by 30% of pramlintide-treated and 27% of rapid-acting insulin analog-treated patients (P=0.83).<br><br>PPG increments were similar between study groups at week 24. No significant difference in the least squares mean change in postprandial increment from baseline to week 24 was found between treatment groups |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | (-17 mg/dl [pramlintide] vs -27 mg/dl [rapid-acting insulin analog]; P=0.17).<br><br>The most common adverse events were hypoglycemia and nausea. Mild or moderate hypoglycemia occurred more frequently than nausea in both study groups and was observed in more patients treated with rapid acting insulin analog (82%) than with pramlintide (55%). Hypoglycemic events occurred more frequently in the pramlintide treatment group in the first 4 weeks but were more common in the rapid acting insulin analog treatment group from 18 to 24 weeks. Nausea was reported only in the pramlintide group (21%), most often early in treatment and declined over time. |

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviation: BMI=body mass index, CI=confidence interval, FPG=fasting plasma glucose, $HbA_{1c}$=glycosylated hemoglobin, PPG=post-prandial glucose

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 9. Relative Cost of the Amylinomimetics**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Pramlintide | injection | Symlin®, SymlinPen® | $$$$$ | N/A |

N/A=Not available

## X. Conclusions

Pramlintide is the only amylinomimetic agent that is currently available. It is approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.[1-3] It is not available in a generic formulation.

Several guidelines provide recommendations on the treatment of type 2 diabetes. According to the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) treatment algorithm, metformin is recommended as first-line therapy, followed by a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist or basal insulin. Notably the higher the glycosylated hemoglobin ($HbA_{1c}$), the more likely insulin will be required.[5] Pramlintide may be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.[7] In general, current clinical guidelines do not support the use of amylin analogs in the management of type 2 diabetes.

For the treatment of type 1 diabetes, the ADA recommends the use of multiple dose insulin injections or continuous subcutaneous insulin infusion therapy. The addition of pramlintide to intensive insulin therapy should be considered to enhance glycemic control and to assist with weight management.[7]

Several clinical trials have been conducted with pramlintide in patients with type 1 and type 2 diabetes mellitus.[17-19,22,25-27] Data from clinical trials demonstrate that treatment with pramlintide is associated with significant baseline reductions in $HbA_{1c}$ compared to treatment with placebo in type 1 and 2 diabetics already receiving insulin.[17-31] Furthermore, treatment with pramlintide is associated with significant baseline reductions in fasting plasma glucose levels, post-prandial glucose levels, insulin use, and body weight.[17-31] However, compared to other available antidiabetic agents, pramlintide is associated with modest $HbA_{1c}$ lowering ability, and its use is often limited by adverse events.[5]

Pramlintide does not cause hypoglycemia when used alone; however, it is intended to be coadministered with insulin therapy. In this setting, pramlintide increases the risk of insulin-induced severe hypoglycemia, especially in patients with type 1 diabetes mellitus.[1] To minimize this risk, patients must be carefully selected, proper education must be provided, and glucose levels must be carefully monitored.[1] Therapy should only be considered in patients with insulin-using type 1or type 2 diabetes who fulfill the following criteria: 1) have failed to achieve adequate glycemic control despite individualized insulin management; and 2) are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).[1]

There is insufficient evidence to support that one brand amylinomimetic is safer or more efficacious than another within its given indication. Since pramlintide is only approved for use as an adjunctive treatment in patients with type 1 and type 2 diabetes mellitus, it should be managed through the existing medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand amylinomimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Biguanides
# AHFS Class 682004
# November 14, 2012

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service (AHFS) classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Metformin in the only biguanide that is currently available and it is approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Insulin secretion remains unchanged; however, fasting insulin levels and daylong plasma insulin response may decrease.[1-6]

The biguanides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Both the immediate-release and sustained-release tablets are available in a generic formulation. This class was last reviewed in May 2010.

**Table 1. Biguanides Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Metformin | Extended-release tablet, solution, tablet | Fortamet®*, Glucophage®*, Glucophage XR®*, Glumetza®, Riomet® | metformin, metformin extended-release |

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Biguanides**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[7] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes<br>• An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[8] (2012)** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy.<br><br>Initial drug therapy<br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br><u>Advancing to dual combination therapy</u><br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.<br>• Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.<br>• It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.<br>• For all medications, consideration should also be given to overall tolerability.<br><br><u>Advancing to triple combination therapy</u><br>• Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.<br>• Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.<br>• In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.<br>• Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.<br><br>**Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations**<br>**Initial Drug Monotherapy**: Metformin<br>Efficacy (↓$HbA_{1c}$): High |

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>
<table>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonyl-urea</td><td>Metformin + thia-zolidinedione (TZD)</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor agonist</td><td>Metformin + insulin (usually basal)</td></tr>
<tr><td>Efficacy (↓$HbA_{1c}$)</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypo-glycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Oedema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td rowspan="2">Three Drug Combin-ations</td><td>Metformin + sulfonyl-urea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td>TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table>
</td></tr>
<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[9] (2012)</td><td>
• Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.<br>
• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.<br>
• It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[10] (2011)</td><td>
<u>Antihyperglycemic pharmacotherapy</u><br>
• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[11]<br>
• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>
• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>
• TZDs and sulfonylureas are examples of oral agents primarily affecting
</td></tr>
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| Clinical Guideline | Recommendation(s) |
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| | FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[11] (2009)** | <u>Principles underlying the algorithm</u><br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action.<br>• Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br><u>Stratification by current $HbA_{1c}$</u><br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered. |

| Clinical Guideline | Recommendation(s) |
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| | • Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br><u>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%</u><br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + GLP-1 receptor agonist + glinide.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + DPP-4 inhibitor + glinide.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia. |

| Clinical Guideline | Recommendation(s) |
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| | • The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + TZD.<br>  o Metformin + sulfonylurea.<br>  o Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>  o Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve |

| Clinical Guideline | Recommendation(s) |
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| | glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>  o Metformin + TZD.<br>  o Metformin + TZD + sulfonylurea.<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[12] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  o $HbA_{1c} \leq 6.5\%$.<br>  o FPG <100 mg/dL.<br>  o Two-hour PPG <140 mg/dL.<br>  o Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>  o Initiate self-monitoring blood glucose levels. |

| Clinical Guideline | Recommendation(s) |
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| | Glycemic management-patients with type 2 diabetes<br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>• First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>• After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>• Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>• Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>• Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration |

| Clinical Guideline | Recommendation(s) |
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| | is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE):<br>**Type 2 Diabetes: Newer Agents[13] (2009)** | <u>DPP-4 inhibitors</u><br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br><u>TZDs</u><br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea |

| Clinical Guideline | Recommendation(s) |
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| | monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  o A body mass index ≥35 kg/m$^2$ in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI <35 kg/m$^2$, and thera$^p$y with insulin would have significant occupational implications or weight loss would benefit other sig$^n$ificant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  o A person prefers injecting insulin immediately before a meal<br>  o Hypoglycemia is a problem.<br>  o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people: |

| Clinical Guideline | Recommendation(s) |
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| | ○ Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>○ Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>○ Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>○ Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>• Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE):<br>**Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[14] (2008)** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br><u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>○ The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>○ A sulfonylurea if metformin is not tolerated.<br>○ Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant. |

| Clinical Guideline | Recommendation(s) |
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| | <u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u><br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/$m^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  o Inadequate blood glucose control ($HbA_{1c}$ ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  o Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin Therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  o Continue with metformin and the sulfonylurea (and acarbose, if used)<br>  o Review the use of the sulfonylurea if hypoglycemia occurs<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>  o Continue with metformin<br>  o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs<br>• Consider combining pioglitazone with insulin therapy for:<br>  o Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>  o Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>  o Those who require assistance from a care taker or healthcare professional to administer their insulin injections<br>  o Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes<br>  o Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ is >9.0%. A once-daily regimen may be an option when initiating |

| Clinical Guideline | Recommendation(s) |
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| | this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>  ○ Immediate injection before a meal is preferred.<br>  ○ Hypoglycemia is a problem.<br>  ○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[15] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |
| International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes[16] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br>Insulin<br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c}$.<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the biguanides are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical

significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Biguanides[1-4]**

| Indication | Metformin |
|---|---|
| Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus | ✔ |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the biguanides are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the Biguanides[5]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|
| Metformin | 50 to 60† | Negligible (% not reported) | Renal (90) | 1.5 to 6.2 (plasma)<br>17.6 (blood) |

†Immediate-release formulations

## V. Drug Interactions

Significant drug interactions with the biguanides are listed in Table 5.

**Table 5. Significant Drug Interactions with the Biguanides[6]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Metformin | 1 | Iodinated contrast materials, parenteral | Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

The most common adverse drug events reported with the biguanides are listed in Table 6. The boxed warnings for metformin-containing products are listed in Tables 7 and 8.

**Table 6. Adverse Drug Events (%) Reported with the Biguanides[1-4]**

| Adverse Events | Metformin Immediate-Release Formulations | Metformin Sustained-Release Formulations |
|---|---|---|
| **Cardiovascular** | | |
| Chest discomfort | - | 1 to 5* |
| Hypertension | - | 1 to 5* |
| Palpitations | 1 to 5 | - |
| **Central Nervous System** | | |
| Asthenia | 9.2 | 1 to 5* |
| Dizziness | - | 1 to 5 |
| Headache | 5.7 | 4.7 to 5 |
| Lightheadedness | 1 to 5 | - |
| **Gastrointestinal** | | |
| Abdominal discomfort | 6.4 | - |
| Abdominal pain | - | 1 to 5 |
| Abnormal stools | 1 to 5 | 1 to 5* |
| Constipation | - | 1 to 5 |

| Adverse Events | Metformin Immediate-Release Formulations | Metformin Sustained-Release Formulations |
|---|---|---|
| Diarrhea | 53.2 | 9.6 to 16.7 |
| Distention abdomen | - | 1 to 5 |
| Dyspepsia/heartburn | - | 1 to 5 |
| Flatulence | 12.1 | 1 to 5 |
| Indigestion | 7.1 | - |
| Loose stools | - | 1 to 5* |
| Nausea/vomiting | 25.5 | 6.5 to 8.5 |
| **Respiratory** | | |
| Dyspnea | 1 to 5 | - |
| Rhinitis | - | 4.2 |
| Upper respiratory infection | - | 1 to 5 |
| **Miscellaneous** | | |
| Accidental injury | - | 5.6 to 7.3 |
| Contusion | - | 1 to 5* |
| Ear pain | - | 1 to 5* |
| Flu syndrome | 1 to 5 | 1 to 5* |
| Hypoglycemia | 1 to 5 | 13.7* |
| Increased sweating | 1 to 5 | - |
| Infection | 20.9 | 20.5, 1 to 5* |
| Myalgia | 1 to 5 | 1 to 5* |
| Nail disorder | 1 to 5 | - |
| Rash | 1 to 5 | - |
| Seasonal allergy | - | 1 to 5* |
| Taste disorder | 1 to 5 | 1 to 5 |
| Toothache | - | 1 to 5* |
| Tonsillitis | - | 1 to 5* |
| Tremor | - | 1 to 5* |

- Event not reported
* Reported with Glumetza®

**Table 7. Boxed Warning for Fortamet®, Glucophage®, Glucophage XR®, and Riomet® (metformin)[1,2,4]**

| WARNING |
|---|
| Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory |

| WARNING |
|---|
| evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/minute under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. |

**Table 8. Boxed Warning for Glumetza® (metformin)[3]**

| WARNING |
|---|
| Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, Glumetza®, should be discontinued and the patient hospitalized immediately. |

## VII. Dosing and Administration

The usual dosing regimens for the biguanides are listed in Table 9.

**Table 9. Usual Dosing Regimens for the Biguanides[1-4]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| Metformin | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Oral solution, tablet: initial, 500 mg BID or 850 mg QD; maintenance, 2,000 mg/day administered in divided doses; maximum, 2,550 mg/day<br><br>Sustained-release tablet (Fortamet®): initial, 500 or 1,000 mg QD; maximum, 2,500 mg/day | Adjunct to diet and exercise to improve glycemic control in children 10 to 16 years of age with type 2 diabetes mellitus:<br>Oral solution, tablet: initial, 500 mg BID; maximum, 2,000 mg/day | Oral solution (Riomet®): 500 mg/5 mL<br><br>Sustained-release tablet:<br>500 mg (Fortamet®, Glucophage XR®, Glumetza®)<br>750 mg (Glucophage XR®)<br>1,000 mg (Fortamet®, Glumetza®) |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | Sustained-release tablet (Glucophage XR®, Glumetza®): initial, 500 mg QD; maximum, 2,000 mg QD | | Tablet (Glucophage®): 500 mg 850 mg 1,000 mg |

BID=twice daily, QD=once daily

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the biguanides are summarized in Table 10.

**Table 10. Comparative Clinical Trials with the Biguanides**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Type 2 Diabetes – Monotherapy** | | | | |
| Jones et al.[17] (2002)<br><br>Metformin 1,000 to 2,000 mg daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 8 to 16 years of age with type 2 diabetes, FPG 7.0 to 13.3 mmol/L, $HbA_{1c}$ ≥7.0%, stimulated C-peptide ≥0.5 nmol/L, and BMI >50th percentile for age | N=82<br><br>16 weeks | Primary:<br>Change in baseline FPG<br><br>Secondary:<br>Change in baseline $HbA_{1c}$, body weight, height, BMI, lipid stimulated C-peptide levels | Primary:<br>Adjusted mean change from baseline in FPG for metformin was -2.4 mmol/L compared to 1.2 mmol/L for placebo (P<0.001).<br><br>Secondary:<br>Mean $HbA_{1c}$ levels, adjusted for baseline levels, were significantly lower for metformin compared to placebo (7.5 vs 8.6%, respectively; P<0.001).<br><br>Mean TC decreased from baseline in the metformin group (-0.25 mmol/L [-9.7 mg/dL]) compared to a slight increase in the placebo group (0.01 mmol/L [0.7 mg/dL]; P=0.043).<br><br>Mean LDL-C decreased more with metformin (-0.11 mmol/L [-4.2 mg/dL] vs -0.10 mmol/L [4 mg/dL]; P=0.053).<br><br>No between-group differences were seen in the mean adjusted changes in HDL-C or TGs.<br><br>Mean weight changes and mean BMI changes from baseline were comparable between the treatment groups.<br><br>There was no between-group difference seen in the adjusted mean stimulated C-peptide change from baseline (-0.2 nmol/L for both groups [-0.7 vs -0.6 ng/mL]).<br><br>The most common reported adverse events were abdominal pain, diarrhea, nausea/vomiting, and headache. Patients receiving metformin experienced more abdominal pain (25%) vs placebo (12%) and more nausea/vomiting (17%) vs placebo (10%). |
| Bhansali et al.[18] (2005) | OL | N=40 | Primary:<br>Changes in four- | Primary:<br>Mean fasting glucose was <120 mg/dL in 80, 63, 73, and 90% of patients |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Month 1:<br>After a lead-in period of 3 months on their usual metformin IR regimen, patients were evaluated (visit 0, baseline) and started on a specific brand of metformin IR at their usual dose, 1,000 to 2,000 mg daily, and continued on this regimen for 1 month until visit 1.<br><br>Month 2:<br>patients were evaluated (visit 1) and changed over to metformin ER as a single dose at dinner, at a dose 500 mg less than the baseline dose of metformin IR; they continued on this regimen for 1 month<br><br>Month 3:<br>patients were evaluated (visit 2) and changed over | Patients ≥40 years of age with type 2 diabetes, BMI ≥20 kg/m$^2$, $HbA_{1c}$ ≤8.5%, and a fasting capillary glucose ≤120 mg/dL who had achieved moderate or good glycemic control with metformin IR alone or in combination with other antihyper-glycemic agents | 7 months (3 month lead-in and 4 month observation) | point glucose profile at each visit and in $HbA_{1c}$ at the end of the study period, changes in weight and lipid profiles, compliance was assessed by reviewing the tablet counts conducted at each study visit and patients were asked to confirm their compliance with therapy at each visit (acceptable compliance was defined as >80% of expected study drug consumption)<br><br>Secondary:<br>Not reported | at visits one, two, three, and four, respectively; these differences were not significant.<br><br>Mean post-breakfast glucose was 149, 165 (P=0.009), 158 (P=0.159), and 159 mg/dL (P=0.111) at visits one, two, three, and four, respectively (P values are when compared to visit one).<br><br>Mean post-lunch glucose was 130, 154 (P=0.003), 151 (P=0.012), and 138 mg/dL (P=0.076) at visits one, two, three, and four, respectively (P values are when compared to visit one).<br><br>Mean post-dinner glucose was 138, 161 (P=0.020), 138 (P=0.967), and 128 mg/dL (P=0.264) at visits one, two, three, and four, respectively (P values are when compared to visit one).<br><br>Mean PPG was 139, 160 (P=0.001), 149 (P=0.065), and 142 mg/dL (P=0.289) at visits one, two, three, and four, respectively (P values are when compared to visit one).<br><br>Mean $HbA_{1c}$ after three months of metformin ER (visit 4) was 6.3% compared to baseline $HbA_{1c}$ of 6.9% with metformin IR (P=0.008). No other $HbA_{1c}$ values were reported. Patients switched over to the ER formulation, once re-established at doses equivalent to their baseline metformin IR doses, and achieved glycemic control comparable to baseline levels.<br><br>Mean weight at the end of three months of metformin ER (visit four) was 68.7±10.2 kg as compared to 69.6±10.8 kg at baseline (P=0.020).<br><br>Lipid profile after three months of metformin XR was the following: mean TC (182±29 mg/dL), LDL-C (113±26 g/dL), HDL-C (45±8 mg/dL), and TG (119±55 mg/dL). These were not statistically significant from baseline.<br><br>Two patients complained of diarrhea and one had loss of appetite and complained of diarrhea during the new metformin XR regimen. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| to metformin XR 1,000 to 2,000 mg daily at bedtime, keeping the dose the same as their baseline metformin IR dose; they continued on this regimen for 1 month<br><br>Month 4:<br>patients were evaluated (visit 3) and changed over to metformin XR 1,000 to 2,000 mg daily in two divided doses keeping the dose the same as baseline metformin IR dose; they continued on this regimen for 1 month<br><br>Patients were evaluated at the end of the study (visit 4). | | | | Secondary:<br>Not reported |
| Blonde et al.[19] (2004)<br><br>Metformin XR 500 to 2,500 mg daily | MC, RETRO<br><br>Patients ≥17 years of age with type 2 diabetes who were started on | N=468<br><br>1 year | Primary:<br>Gastrointestinal tolerability and frequency of diarrhea for metformin XR | Primary:<br>Overall metformin XR vs metformin IR cohorts:<br>The frequency of gastrointestinal events was similar between metformin XR and metformin IR (11.94 vs 11.39%, respectively; P=0.86).<br><br>The RR of any gastrointestinal adverse event for metformin XR compared |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>metformin IR 500 to 2,500 mg daily | metformin XR (Glucophage XR®), or switched from metformin IR or another oral antidiabetic agent to metformin XR within the previous 2 years | | compared to metformin IR during the first year of treatment<br><br>Secondary:<br>Not reported | to metformin IR was 1.05 (95% CI, 0.62 to 1.78).<br><br>The percentages of patients with individual gastrointestinal adverse events in the metformin XR and metformin IR groups, respectively were as follows: diarrhea (6.77 vs 7.59%), nausea (2.26 vs 3.80%), dyspepsia (1.61 vs 1.27%), abdominal pain (1.61 vs 0.63%), constipation (0.97 vs 0.63%), vomiting (0.65 vs 0.63%), abdominal distention (0.32 vs 0.00%), fecal abnormality (0.32 vs 0.63%), blood in stools (0.00 vs 063%), and flatulence (0.00 vs 0.63%).<br><br>Patients switched from metformin IR to metformin XR:<br>Significantly more patients experienced a gastrointestinal adverse event during the first year of treatment with metformin IR (26.34%, 54/205; P=0.006) than after switching to metformin XR (11.71%, 24/205). The mean daily dose of metformin XR was 1,184 mg (range, 500 to 2,500 mg) during the first year of therapy and 1,047 mg (range, 500 to 2,550 mg) for the metformin IR groups.<br><br>A significantly higher percentage of patients reported diarrhea (18.05%, 37/205) while taking metformin IR than after switching to metformin XR (8.29%, 17/205; P=0.0084).<br><br>More patients reported nausea (2.93%), dyspepsia (3.41%), abdominal distention (2.44%), and flatulence (2.44%) while taking the metformin IR than after switching to metformin XR (1.95, 1.46, 0.49, and 0.0%, respectively); however, the differences were not significant.<br><br>Patients new to metformin XR vs metformin IR:<br>A greater percent of patients reported a gastrointestinal adverse event during the first year of treatment with metformin IR (19.83%, 72/363) than during the first year of therapy with metformin XR (9.23%, 6/65; P=0.0414).<br><br>A greater percent of patients taking metformin IR reported diarrhea (13.5%, 49/363) as compared to the metformin XR group (3.08%, 2/65; P=0.0169). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Secondary:<br>Not reported |
| Fujioka et al.[20] (2003)<br><br>Metformin XR (Glucophage XR®) 1,000 mg QD with the evening meal<br><br>vs<br><br>metformin XR 1,000 mg QD with the evening meal for 1 week, then increased to 1,500 mg QD<br><br>vs<br><br>continued metformin IR 500 mg BID<br><br>Note: after 12 weeks, the daily dose of metformin could be increased by 500 mg in any group if $HbA_{1c}$ was ≥8.0% at that time. | DB, MC, PG, RCT<br><br>Patients to 27 to 77 years of age with type 2 diabetes for >2 months to <10 years, $HbA_{1c}$ ≤8.5%, FPG ≤200 mg/dL, and receiving metformin IR 500 mg BID for ≥8 weeks | N=217<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$ from baseline to week 12 with the switch from metformin IR to metformin XR<br><br>Secondary:<br>Change in baseline $HbA_{1c}$ to week 24, changes in FPG, mean daily blood glucose concentrations, fructosamine, serum insulin levels, lipid levels, body weight, safety | Primary:<br>Mean changes from baseline in $HbA_{1c}$ values at week 12 were small and similar in the three treatment groups. At week 12, the mean change from baseline was 0.15% for metformin IR, 0.23% for metformin XR 1,000 mg, and 0.04% for metformin XR 1,500 mg.<br><br>Secondary:<br>The corresponding changes in $HbA_{1c}$ values at week 24 were small and similar among the three treatment groups: 0.06% for metformin IR, 0.25% for metformin XR 1,000 mg, and 0.14% for metformin XR 1,500 mg. The distribution of $HbA_{1c}$ values in the specified categories (<7.0, 7.0 to <8.0, and ≥8.0%, respectively) was not significant between the groups during the study.<br><br>Mean FPG concentrations had also increased in all three treatment groups at week 12 and 24. The mean increases were smaller in the metformin XR groups compared to the metformin IR group.<br><br>No clinically relevant significant changes from baseline were seen in HDL-C or TC levels in any treatment group. LDL-C decreased in all treatment groups, with a mean change of -4 mg/dL in the metformin IR group (95% CI, -9 to 1), and -6 mg/dL in both XR groups (1,000 mg XR, 95% CI, -11 to -1; 1,500 mg XR, 95% CI, -12 to 0). There were small increases from baseline in TG levels in patients receiving metformin IR (mean change, 1 mg/dL; 95% CI, -14 to 17). There were significant increases in TGs in patients receiving metformin XR. Patients in the 1,000 mg group had an increase of 34 mg/dL (95% CI, 15 to 53) and patients in the 1,500 mg group had an increase of 42 mg/dL (95% CI, 6 to 78).<br><br>Mean daily blood glucose concentration, fructosamine, serum insulin levels, and body weight showed similar changes in each group.<br><br>Twenty-five percent of patients in the metformin IR group, 29% of patients in the metformin XR 1,000 mg group, and 34% of patients in the metformin XR 1,500 mg group experienced adverse drug events |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | (occurring in ≥3% of patients). Diarrhea, flatulence, abdominal pain, and nausea/vomiting were the most common adverse events reported among all groups combined. Three percent of metformin IR, 5% of metformin XR 1,000 mg, and 15% of metformin 1,500 mg patients experienced diarrhea. Flatulence was reported in 1% of metformin IR patients, 4% of metformin XR 1,000 mg patients, and 3% of metformin XR 1,500 mg patients. Abdominal pain was reported in 1% of metformin IR patients and metformin XR 1,500 mg patients and in 4% of metformin XR 1,000 mg patients. Nausea/vomiting were reported in 4% of metformin IR patients and 3% in both metformin XR groups. Headache was reported in 4% of metformin IR and metformin XR 1,000 mg patients. Dyspepsia/heartburn was reported in 6% of metformin IR and 3% of metformin XR 1,000 mg patients. The study was not statistically powered to detect differences in tolerability between the groups. |
| Schwartz et al.[21] (2006)<br><br>Metformin XR 1,500 mg QD<br><br>vs<br><br>metformin XR 1,500 mg daily in 2 divided doses<br><br>vs<br><br>metformin XR 2,000 mg QD<br><br>vs<br><br>metformin IR 1,500 mg daily in 2 divided doses | AC, DB, MC, RCT<br><br>Patients 18 to 79 years of age with type 2 diabetes, $HbA_{1c}$ 7.0 to 12.0% (drug-naïve patients) or 6.5 to 10.0% (prior drug therapy patients), FPG 120 to 400 mg/dL (drug-naïve patients) or 120 to 250 mg/dL (prior drug therapy patients), C-peptide levels >1 ng/mL, and BMI 22 to 50 $kg/m^2$ | N=750<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, fructosamine, TC, HDL-C, LDL-C, and TG | Primary:<br>Reductions in mean $HbA_{1c}$ were significant by week 12 for all groups, continued to decline until week 20, and were maintained for the duration of the study. The change from baseline was significant for each group (P<0.001).<br><br>Mean changes in $HbA_{1c}$ from baseline to end point in all metformin XR groups were similar to the metformin IR groups. Mean changes in $HbA_{1c}$ from baseline to end point in the two groups given 1,500 mg metformin XR (-0.73% and -0.74%) were not significantly different from the change in the metformin IR group (-0.70%), whereas the 2,000 mg metformin XR group showed a greater decrease in $HbA_{1c}$ levels (-1.06%).<br><br>Secondary:<br>Reductions in mean FPG were significant in all groups by the end of week one, declined until week eight, and these levels were maintained until the end of the study. The change from baseline was significant for each group (P<0.001). The mean changes from baseline to end point within each of the metformin XR groups were comparable with or greater than that in the metformin IR group (P=0.051 for overall comparison among groups).<br><br>Mean fructosamine levels decreased from baseline within all groups. There was a significant difference among groups for fructosamine levels at |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | the end point, with the lowest level observed with the 2,000 mg once daily metformin XR group.<br><br>TC, LDL-C, and HDL-C levels were similar at baseline and end point with all treatment groups, except for differences with treatment groups for final LDL-C (P=0.015) and TG (P=0.030). The lowest mean concentrations for LDL-C and TG occurred with 2,000 mg QD metformin XR and metformin IR, respectively.<br><br>Overall incidence of gastrointestinal adverse events was low and comparable among treatment groups during the first week of treatment. There was a higher incidence of nausea in the metformin IR group than in the metformin XR groups (P=0.05) during the first week.<br><br>Overall incidence of adverse events considered possibly or probably related to the study drug was similar for all groups. The only events reported for >5% of patients in any group during the entire study were gastrointestinal (diarrhea, nausea, dyspepsia, upper abdominal pain). |
| Pavo et al.[22] (2003)<br><br>Metformin 850 to 2,550 mg daily<br><br>vs<br><br>pioglitazone 30 to 45 mg daily | DB, MC, RCT<br><br>Recently diagnosed (<12 months) type 2 diabetic patients ≥40 years of age, $HbA_{1c}$ of 7.5 to 11.0%, and naïve to oral antihyperglycemic medications | N=205<br><br>32 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Changes in FPG, fasting serum insulin, and insulin sensitivity | Primary:<br>Each treatment group had a significant reduction in $HbA_{1c}$ from baseline (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.280).<br><br>Secondary:<br>Each treatment group had a significant reduction in FPG (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.620).<br><br>Pioglitazone reduced fasting serum insulin significantly (P<0.0001). The change in fasting serum insulin was not significant for metformin (P=0.803).<br><br>Pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of HOMA-S (P=0.002). |
| Cryer et al.[23] (2005) | MC, OL, PG, RCT | N=8,732 | Primary:<br>Incidence of | Primary:<br>Serious adverse reactions were reported in 10.3% (95% CI, 9.6 to 11.1) of |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Metformin 500 mg BID to 2,500 mg daily in 3 divided doses<br><br>vs<br><br>usual care | Type 2 diabetic patients ≥18 years old with glycemia inadequately controlled with diet or a sulfonylurea | 1 year | serious adverse events, death, hospitalization<br><br>Secondary:<br>Plasma lactate levels after one year of treatment in a substudy | patients in the metformin group and by 11.0% (95% CI, 9.5 to 12.7) of patients in the usual care group (P=0.43), with similar pattern of serious adverse events between groups according to body system. Serious cardiovascular adverse events were the most common, which included coronary artery disease (1.0 vs 1.1%) for metformin vs usual care, respectively, chest pain (0.7 vs 1.0%), congestive heart failure (0.7 vs 0.6%), MI (0.7 vs 0.7%), and cerebrovascular accident (0.4 vs 0.7%). There was not an excess of serious adverse events observed in the metformin group in all patients regardless of age.<br><br>The incidence of all-cause hospitalization, hospitalization for metabolic causes (other than lactic acidosis), and all-cause mortality did not differ between metformin and usual care in the overall population (P=0.229, P=1.0, P=0.596, respectively) or in patients ≥65 years old (P=0.178, P=1.0, P=0.878, respectively), or in younger patients (P=0.945, P=0.835, P=0.21, respectively). There were no patients that were hospitalized or that died from lactic acidosis.<br><br>Secondary:<br>Mean plasma lactate was 1.7±0.6 mmol/L in the metformin group and 1.6±0.6 mmol/L in the usual care group after 12 months of therapy (P=0.137). Plasma lactate >3 mmol/L occurred in 4% of metformin patients and 1% in the usual care group. There was no significant difference between the groups. |
| Gottschalk et al.[24] (2007)<br><br>Metformin 500 to 1,000 mg BID<br><br>vs<br><br>glimepiride 1 to 8 mg QD | AC, MC, PG, SB, RCT<br><br>Pediatric subjects 8 to 17 years of age with type 2 diabetes ($HbA_{1c}$ >7.1 and <12.0%) with inadequate control despite treatment with either diet and exercise alone for at least 2 weeks prior | N=285<br><br>24 weeks | Primary:<br>Mean change in $HbA_{1c}$ from baseline to week 24<br><br>Secondary:<br>Mean change in $HbA_{1c}$ from baseline to week 12, proportion of patients achieving an $HbA_{1c}$ <7.0% at | Primary:<br>Significant reductions from baseline $HbA_{1c}$ were seen in both the glimepiride (−0.54%; P=0.001) and metformin (−0.71%; P=0.0002) groups. No significant differences were observed between groups in reductions in $HbA_{1c}$.<br><br>Secondary:<br>Significant reductions in the adjusted mean change from baseline $HbA_{1c}$ to week 12 were –0.69 and –0.76% in patients receiving glimepiride and metformin, respectively (P<0.05).<br><br>A total of 42.4 and 48.1% of patients in the glimepiride and metformin groups, respectively, achieved $HbA_{1c}$ <7.0% at week 24 (P=0.347). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | to randomization or diet and exercise combined with 3 months of ongoing or previous oral antidiabetic monotherapy | | week 24, mean change in fasting self-monitoring of blood glucose from baseline to weeks four, eight, 12, 18, and 24, mean changes in serum lipid concentrations from baseline to week 24 and changes in BMI, safety, adverse events, hypoglycemic episodes and vital signs | Significant reductions were seen in fasting self-monitoring of blood glucose levels from baseline to weeks 18 and 24 in patients receiving metformin (P<0.05) but no similar reductions were reported in the glimepiride group.<br><br>There were no significant differences between the glimepiride and metformin groups in the mean change from baseline in any of the serum lipid concentrations.<br><br>Significant between-group differences were observed in the mean change from baseline BMI to week 24. Values were 0.26 and 0.33 $kg/m^2$ in patients receiving glimepiride and metformin, respectively (P=0.003).<br><br>No deaths occurred during the study. The proportions of patients experiencing ≥1 adverse event were comparable between both treatment groups, with the most common adverse events being hyperglycemia, upper abdominal pain, diarrhea, nausea and headache. Two patients experienced serious adverse events that were considered possibly related to treatment: one patient in the glimepiride group had hyperglycemia, diabetic ketoacidosis and increased serum osmolarity and one patient in the metformin group had a non-hypoglycemic convulsion.<br><br>The incidence of clinically relevant hypoglycemia was similar in both groups (P=0.554).<br><br>No clinically significant differences in vital signs were seen between treatment groups. |
| Lund et al.[25] (2008)<br><br>Repaglinide 2 mg TID for 4 months<br><br>vs | DD, XO<br><br>Non-obese (BMI ≤27 $kg/m^2$), insulin-naïve patients with type 2 diabetes mellitus | N=96<br><br>8 months with 1 month washout | Primary:<br>Cardiovascular disease biomarkers and metabolic regulation<br><br>Secondary:<br>Not reported | Primary:<br>Levels of TNF-α, plasminogen activator inhibitor-1 antigen, tissue-type plasminogen activator antigen, von Willebrand factor, soluble intercellular adhesion molecule-1 and soluble E-selectin were significantly lower during metformin treatment compared with repaglinide treatments.<br><br>Amadori albumin and heart rate were higher during metformin compared with repaglinide. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| metformin<br>1,000 mg BID for 4 months | | | | Both treatment groups experienced similar levels of interleukin-6, fibrinogen, soluble vascular cell adhesion molecule-1, asymmetric dimethylarginine and advanced glycation end products as well as glycemic levels and 24 hour BP.<br><br>Secondary:<br>Not reported |
| Lund et al.[26]<br>(2008)<br><br>Repaglinide<br>2 mg TID for 4 months<br><br>vs<br><br>metformin<br>1,000 mg BID for 4 months | DD, XO<br><br>Non-obese (BMI ≤27 kg/m$^2$), insulin-naïve patients with type 2 diabetes mellitus | N=192<br><br>8 months with 1 month washout | Primary:<br>Postprandial metabolism with blood sampling 0 to six hours postprandially<br><br>Secondary:<br>Not reported | Primary:<br>Both treatment groups equally changed fasting levels and total AUC for plasma glucose, TGs and FFA.<br><br>The metformin treatment group obtained lower fasting levels and AUC of TC, LDL-C, and non-HDL-C and serum insulin compared with repaglinide. After adjusting for fasting levels, AUC differences still remained significant.<br><br>Secondary:<br>Not reported |
| Sullivan et al.[27]<br>(2011)<br>FIELD<br><br>Metformin<br><br>vs<br><br>sulfonylurea<br><br>vs<br><br>diet alone | PRO<br><br>Patients with type 2 diabetes | N=6,005<br><br>5 years | Primary:<br>Cardiovascular disease outcomes<br><br>Secondary:<br>Hypoglycemic therapy | Primary:<br>Patients receiving monotherapy with either metformin or a sulfonylurea appeared to be at greater risk of cardiovascular disease compared to those on diet alone, but results were only significant for the sulfonylurea group, ranging from 42% higher risk of coronary revascularization to a doubled risk of coronary heart disease death. However, adjustment for the duration and intensity of diabetes and the severity of other cardiovascular risk factors abolished the significance of this effect. Total revascularization and total mortality were significantly higher in the sulfonylurea group compared to the metformin group, but all differences became non-significant on adjustment.<br><br>Secondary:<br>Use of oral hypoglycemic agents increased progressively as the trial proceeded. Over five years, treatment with diet alone decreased from 31 to 15%, and dual therapy with metformin plus a sulfonylurea increased from 29 to 36%. Insulin therapy was introduced at a rate of 4% per year. Metformin monotherapy declined from 21 to 18% but the sulfonylurea |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | monotherapy rate declined from 20 to 12%. Patients on sulfonylurea monotherapy were more likely to progress to dual therapy. |
| Kahn et al.[28] (2006)<br><br>Metformin 500 to 1,000 mg BID<br><br>vs<br><br>rosiglitazone 4 mg QD to 4 mg BID<br><br>vs<br><br>glyburide 2.5 to 7.5 mg BID | DB, MC, RCT<br><br>Recently diagnosed (within 3 years) type 2 diabetic patients between 30 to 75 years of age who had not received previous pharmacologic treatment, with FPG levels ranging from 126 to 180 mg/dL while their only treatment was lifestyle management | N=4,360<br><br>4 to 6 years (median treatment durations 3.3 years for glyburide and 4 years for rosiglitazone and metformin) | Primary:<br>Time from randomization to treatment failure (defined as FPG >180 mg/dL on consecutive testing after at least six weeks of treatment at the maximum tolerated dose)<br><br>Secondary:<br>Time from randomization to a confirmed FPG >140 mg/dL after at least six weeks of treatment at the maximum tolerated dose (for patients who entered the study with FPG ≤140 mg/dL); FPG, $HbA_{1c}$, weight, measures of insulin sensitivity, β-cell function, and adverse events | Primary:<br>At five years, 15% of patients receiving rosiglitazone, 21% of those on metformin, and 34% of those on glyburide had failed monotherapy. This represents a risk reduction of 32% for rosiglitazone as compared with metformin and 63% for rosiglitazone as compared with glyburide (P<0.001 for both comparisons).<br><br>Secondary:<br>Progression to a confirmed FPG ≥140 mg/dL was seen in 79 of 511 patients in the rosiglitazone group as compared with 127 of 520 patients in the metformin group (P=0.002) and 160 of 480 patients in the glyburide group (P<0.001).<br><br>At the four-year evaluation, 40% of the patients in the rosiglitazone group achieved an $HbA_{1c}$ <7.0% compared with 36% of the patients in the metformin group (P=0.03) and 26% of the patients in the glyburide group (P<0.001).<br><br>The annual rate of β-cell function decline after six months was greatest in the glyburide group (6.1% decreased), followed by the metformin group (3.1% decreased) and rosiglitazone group (2.0% decreased) (P<0.001 for rosiglitazone vs glyburide and P=0.02 for rosiglitazone vs metformin).<br><br>Over a period of five years, the mean weight increased in the rosiglitazone group but decreased in the metformin group. In the glyburide group, weight gain occurred in the first year then remained stable.<br><br>Treatment with glyburide was associated with lower risk of cardiovascular events (including congestive heart failure) than was seen in the rosiglitazone and metformin groups (P<0.05). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide, but fewer gastrointestinal events were reported with rosiglitazone compared to metformin and fewer hypoglycemic events were seen with rosiglitazone compared to with glyburide (P<0.001 for all comparisons). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Aschner et al.[29] (2010)<br><br>Metformin 1,000 mg BID<br><br>vs<br><br>sitagliptin 100 mg QD | AC, DB, RCT<br><br>Patients 18 to 78 years of age with type 2 diabetes mellitus who were treatment naïve with an $HbA_{1c}$ of 6.5 to 9.0% | N=1,050<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Proportions of patients with $HbA_{1c}$ <7.0% or <6.5%, change in FPG, fasting serum insulin, fasting serum proinsulin, and lipid parameters | Primary:<br>In the per protocol population, the change in $HbA_{1c}$ (least squares mean) from baseline at week 24 was -0.43% in the sitagliptin group and -0.57% in the metformin group (difference, 0.14%; 95% CI, 0.06 to 0.21), which demonstrated the non-inferiority of sitagliptin to metformin.<br><br>In the full analysis set, the $HbA_{1c}$ change from baseline at week 24 was -0.38% (95% CI, -0.43 to -0.32) in the sitagliptin group and -0.55% (95% CI, -0.61 to -0.50) in the metformin group (difference, 0.18%; 95% CI, 0.10 to 0.25), which demonstrated the non-inferiority of sitagliptin to metformin.<br><br>Secondary:<br>The proportion of patients with an $HbA_{1c}$ <7.0% at week 24 was greater with metformin (76%) compared with sitagliptin (69%; difference, -7.1%; 95% CI, -12.9 to -1.2).<br><br>The proportion of patients with an $HbA_{1c}$ <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups (difference, -5.6%; 95% CI, -11.8 to 0.8).<br><br>The change from baseline in FPG was greater with metformin (-19.4 mg/dL compared with sitagliptin (-11.5 mg/dL).<br><br>The reduction in fasting proinsulin was greater in the metformin group, which resulted in a larger reduction in the proinsulin/insulin ratio at week 24.<br><br>Both treatments produced similar increases in β-cell function and reductions in insulin resistance over 24 weeks.<br><br>HDL-C was improved with both treatments. TGs were slightly reduced with sitagliptin. Small increases in TC were observed for each group, with a slightly greater increase for sitagliptin. Modest increases in LDL-C and non-HDL-C were observed with sitagliptin, but not metformin over 24 weeks. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | The incidence of drug-related adverse events was lower in the sitagliptin group than in the metformin group. The incidence of gastrointestinal adverse events overall was lower in the sitagliptin group compared with the metformin group (11.6 vs 20.7%, respectively). Hypoglycemia occurred at a low rate in both groups (1.7% with sitagliptin and 3.3% with metformin; P=0.116). Body weight was reduced from baseline in both the sitagliptin (-0.6 kg) and metformin (-1.9 kg; P<0.001). |
| Nichols et al.[30] (2007)<br><br>Metformin<br><br>vs<br><br>sulfonylurea<br><br>vs<br><br>insulin<br><br>vs<br><br>TZDs | MC, OS, RETRO<br><br>Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies | N=9,546<br><br>≥12 months | Primary:<br>Weight changes<br><br>Secondary:<br>Not reported | Primary:<br>Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.<br><br>Secondary:<br>Not reported |
| Russell-Jones et al.[31] (2012)<br>DRUATION-4<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>metformin 2,000 mg/day | DB, DD, MC, PG, RCT<br><br>Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with $HbA_{1c}$ 7.1 to 11.0%, BMI 23 to 45 kg/m$^2$, and stable | N=820<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid | Primary:<br>Decreases in $HbA_{1c}$ were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The $HbA_{1c}$ at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively.<br><br>Secondary:<br>Similar proportions of patients receiving exenatide ER and metformin achieved $HbA_{1c}$ <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved $HbA_{1c}$ <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>pioglitazone 45 mg/day<br><br>vs<br><br>sitagliptin 100 mg/day | weight | | profile, insulin profile, safety and tolerability, patient-reported QOL | P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001).<br><br>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26).<br><br>Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.<br><br>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892).<br><br>No clinically significant changes in serum lipids were observed with any treatment.<br><br>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329).<br><br>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.<br><br>All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported). |
| Simpson et al.[32] (2006)<br><br>First-generation sulfonylurea<br><br>vs<br><br>glyburide<br><br>vs<br><br>metformin | RETRO<br><br>New users of one oral diabetic agent | N=5,95<br><br>~4.6 years | Primary:<br>Mortality<br><br>Secondary:<br>Not reported | Primary:<br>An increased risk of death was associated with higher daily doses of first-generation sulfonylureas (adjusted HR, 2.1; 95% CI, 1.0 to 4.7) and glyburide (HR, 1.3; 95% CI, 1.2 to 1.4) compared to metformin (HR, 0.8; 95% CI, 0.7 to 1.1).<br><br>Secondary:<br>Not reported |
| Bolen et al.[33] (2007)<br><br>Biguanides<br><br>vs<br><br>meglitinides<br><br>vs<br><br>TZDs | MA (Analysis of 216 controlled trials and cohort studies, and 2 SR)<br><br>Patients with type 2 diabetes | N=136 (articles on intermediate outcomes)<br><br>N=167 (articles on adverse events)<br><br>N=68 (articles on | Primary:<br>Intermediate outcomes: $HbA_{1c}$, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes | Primary:<br>Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in $HbA_{1c}$ level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.<br><br>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>α-glucosidase inhibitors<br><br>vs<br><br>second-generation sulfonylureas | | microvascular outcomes and mortality)<br><br>Duration varied | Secondary:<br>Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events | TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.<br><br>Most agents except metformin increased body weight by 1 to 5 kg.<br><br>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05).<br><br>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).<br><br>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.<br><br>Secondary:<br>According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).<br><br>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.<br><br>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.<br><br>According to a SR of 176 comparative trials, lactic acidosis events were |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | similar between metformin and other oral diabetes agents. |
| Saenz et al.[34] (2005)<br><br>Metformin monotherapy<br><br>vs<br><br>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin | MA (29 RCTs)<br><br>Adult patients with type 2 diabetes | N=5,259<br><br>≥3 months | Primary:<br>Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality<br><br>Secondary:<br>Changes in $HbA_{1c}$, FPG, quality of life, weight, BMI, | Primary:<br>Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).<br><br>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02).<br><br>Secondary:<br>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for $HbA_{1c}$ when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow | |
| Monami et al.[35] (2008)<br><br>Metformin<br><br>vs<br><br>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists | MA<br><br>Patients with type 2 diabetes mellitus | N=7,890 (27 RCT)<br><br>Variable duration | Primary:<br>Reduction in $HbA_{1c}$ at 16 to 36 months<br><br>Secondary:<br>Not reported | Primary:<br>Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in $HbA_{1c}$ by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.<br><br>In direct comparisons, sulfonylureas led to a greater reduction in $HbA_{1c}$ (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.<br><br>Secondary:<br>Not reported |
| Amori et al.[36] (2007)<br><br>Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin†)<br><br>vs<br><br>non-incretin-based therapy (placebo or hypoglycemic agent) | MA (29 RCTs)<br><br>Type 2 diabetics | N=12,996<br><br>Duration varied (12 to 52 weeks) | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, proportion of patients achieving an $HbA_{1c}$ <7.0% | Primary:<br>Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in $HbA_{1c}$ favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81).<br><br>Specifically, no difference in the $HbA_{1c}$ was found in OL, non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar $HbA_{1c}$ efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported).<br><br>Secondary:<br>Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21).<br><br>Exenatide-treated patients were more likely to achieve an $HbA_{1c}$ <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported. |
| Frederich et al.[37] (2010)<br><br>Saxagliptin 2.5 to 10 mg QD<br><br>vs<br><br>glyburide, metformin, or placebo | SR<br><br>Inadequately controlled type 2 diabetics | N=4,607<br><br>16 to 116 weeks | Primary:<br>Composite of cardiovascular events, cardiovascular death, MI, and stroke<br><br>Secondary:<br>Not reported | Primary:<br>There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63).<br><br>Secondary:<br>Not reported |
| Singh et al.[38] (2011)<br><br>TZDs (pioglitazone, rosiglitazone)<br><br>vs<br><br>placebo, sulfonylurea, or metformin | MA, SR (13 RCTs)<br><br>Type 2 diabetics | N=17,627<br><br>1 to 5.5 years (follow-up) | Primary:<br>Any pneumonia or lower respiratory tract infection reported as an adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event<br><br>Secondary:<br>Not reported | Primary:<br>TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02).<br><br>Secondary:<br>Not reported |
| Louisa et al.[39] (2011)<br><br>TZDs (pioglitazone, rosiglitazone)<br><br>vs | MA (37 RCTs)<br><br>Type 2 diabetics | N=3,000<br><br>>3 months | Primary:<br>Glycemic outcomes<br><br>Secondary:<br>Change in baseline BMI, lipid profile, BP, high- | Primary:<br>Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased $HbA_{1c}$. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased $HbA_{1c}$ compared to placebo and a sulfonylurea.<br><br>Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and |

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| placebo or other hypoglycemic agents | | | sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints | rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose†, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea.<br><br>Secondary:<br>Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14).<br><br>Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41).<br><br>Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs.<br><br>Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect.<br><br>In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in high sensitivity CRP.<br><br>Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone.<br><br>Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87). |
| Richter et al.[40] (2006)<br><br>Pioglitazone | MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, | 22 trials<br><br>N=6,200 randomized to | Primary:<br>Patient-oriented outcomes including | Primary:<br>Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, |

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| monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)<br><br>or<br><br>pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)<br><br>Some studies had more than 1 treatment arm. | included PROactive Study), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | pioglitazone treatment (total N not reported)<br><br>24 weeks to 34.5 months | mortality, morbidity, adverse effects<br><br>Secondary: Health-related quality of life, $HbA_{1c}$ | endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).<br><br>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).<br><br>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 $kg/m^2$. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.<br><br>Secondary:<br>No study investigated health-related quality of life.<br><br>Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to pioglitazone treatment (P values not reported). |
| Lincoff et al.[41] (2007) | DB, MA, RCT with placebo or active comparator | N=16,390 (19 trials) | Primary: Composite of death from any cause, MI | Primary:<br>Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Pioglitazone monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial)<br><br>or<br><br>pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo | Adult patients with type 2 diabetes and inadequate glycemic control | 4 months to 3.5 years | or stroke<br><br>Secondary:<br>Incidence of serious heart failure | (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005).<br><br>Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09).<br><br>Progressive separation of time-to-event curves became apparent after approximately one year of therapy.<br><br>Secondary:<br>Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17). |
| Lago et al.[42] (2007)<br><br>Pioglitazone 15 to 45 mg/day (2 trials) or rosiglitazone 4 to 8 mg/day (5 trials)<br><br>vs<br><br>placebo (4 trials), glibenclamide* (1 trial), glimepiride (1 trial), metformin (1 trial), or metformin plus nonspecified | MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and cardiovascular death<br><br>Patients with prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m$^2$, mean baseline | 7 trials<br><br>N=20,191<br><br>29.7 months (range, 12 to 48 months) | Primary:<br>Development of congestive heart failure, risk of cardiovascular death<br><br>Secondary:<br>Not reported | Primary:<br>Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group.<br><br>Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07).<br><br>The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to |

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| sulfonylurea (1 trial)<br><br>Doses of comparators were not specified and 1 trial had 2 control groups. | $HbA_{1c}$ 7.72% | | | 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96).<br><br>Secondary:<br>Not reported |
| Mannucci et al.[43] (2008)<br><br>Pioglitazone<br><br>vs<br><br>active comparators, placebo, no treatment | MA (94 trials)<br><br>Patients treated with pioglitazone (with or without type 2 diabetes) | N=21,180<br><br>Variable duration | Primary:<br>All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary re-vascularization), non-fatal chronic heart failure requiring hospitalization<br><br>Secondary:<br>Not reported | Primary:<br>In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported).<br><br>In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients.<br><br>In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72).<br><br>When analyzing all trials, no significant reduction of mortality was observed with pioglitazone.<br><br>Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45).<br><br>In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported).<br><br>In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23).<br><br>Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant.<br><br>In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98).<br><br>Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure.<br><br>In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance.<br><br>Secondary:<br>Not reported |
| Nagajothi et al.[44] (2008)<br><br>Pioglitazone<br><br>vs<br><br>active comparators (metformin and/or sulfonylurea) or placebo | MA (5 trials)<br><br>Patients treated with pioglitazone | N=not reported<br><br>Duration varied | Primary:<br>MI<br><br>Secondary:<br>Stroke, revascularization, total mortality, cardiovascular mortality | Primary:<br>The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17).<br><br>Secondary:<br>The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07).<br><br>The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56).<br><br>The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11.<br><br>The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Karter et al.[45] (2005)<br><br>Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies | Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001 | N=23,440<br><br>10.2 months (mean) | Primary:<br>Time-to-incident admission to hospital for congestive heart failure<br><br>Secondary:<br>Not reported | Primary:<br>Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99).<br><br>Secondary:<br>Not reported |
| Singh et al.[46] (2007)<br><br>Rosiglitazone<br><br>vs<br><br>control (placebo or other non-TZD oral hypoglycemic drug including glyburide or metformin) | MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration<br><br>Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical data on all adverse events | 4 trials<br><br>N=14,291 (n=6,421 rosiglitazone; n=7,870 control)<br><br>1 to 4 years | Primary:<br>RR of MI, heart failure, and cardiovascular mortality<br><br>Secondary:<br>Not reported | Primary:<br>Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control.<br><br>There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53).<br><br>Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92).<br><br>Secondary:<br>Not reported |
| Nissen et al.[47] (2007) | MA of RCTs of more than 24 weeks | 42 trials | Primary:<br>MI and death from | Primary:<br>Rosiglitazone was associated with a significant increase in the risk of MI |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Rosiglitazone monotherapy or combination therapy<br><br>vs<br><br>placebo or active comparators (including gliclazide†, glimepiride, glipizide, glyburide, insulin, and metformin) | that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials)<br><br>Mean age of participants was 56 years, mean baseline $HbA_{1c}$ 8.2% | n=15,560 for rosiglitazone; n=12,283 for comparator<br><br>24 to 208 weeks | cardiovascular causes<br><br>Secondary:<br>Not reported | compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03).<br><br>Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06).<br><br>Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24).<br><br>Secondary:<br>Not reported |
| Richter et al.[48] (2007)<br><br>Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial)<br><br>or<br><br>rosiglitazone combination therapy vs a similar combination with | MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | 18 trials<br><br>N=3,888 randomized to rosiglitazone treatment (total N not reported)<br><br>24 weeks to 4 years (median 26 weeks) | Primary:<br>Patient-oriented outcomes including mortality, morbidity, adverse effects<br><br>Secondary:<br>Health-related QOL, metabolic control ($HbA_{1c}$) | Primary:<br>No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference).<br><br>The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).<br><br>The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious |

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| another compound (8 trials)<br><br>Some studies had more than 1 treatment arm. | | | | adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 $kg/m^2$. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).<br><br>Secondary:<br>No study investigated health-related quality of life.<br><br>Active glucose-lowering compounds like metformin, glibenclamide* or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to rosiglitazone treatment. |
| **Type 2 Diabetes – Combination Therapy** | | | | |
| Halimi et al.[49] (2000)<br><br>Metformin 850 mg BID to TID and acarbose 50 to 100 mg TID<br><br>vs<br><br>metformin 850 mg BID to TID | DB, PC, PG, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes, BMI 25 to 35 $kg/m^2$, having poor glycemic control despite receiving metformin ≥2 months before the study start | N=152<br><br>6 months | Primary:<br>$HbA_{1c}$ at trial end<br><br>Secondary:<br>Blood glucose, insulin profiles, TG | Primary:<br>Mean difference in $HbA_{1c}$ from baseline to trial end was -0.7±1.2% with acarbose compared to 0.2±1.3% with placebo (P=0.0001).<br><br>Patients were classified as responders if their $HbA_{1c}$ values at trial end were <7.0% or had decreased by <15% relative to baseline. The total numbers of responders were 25 of 49 (42%) patients receiving acarbose and 12 of 70 (17%) patients receiving placebo (P=0.002).<br><br>Secondary:<br>Mean difference in the fasting blood glucose level from baseline to trial end was -1.0±2.8 mmol/L with acarbose compared to 1.3±2.8 mmol/L |

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| | | | | with placebo (P=0.0001).<br><br>Mean difference in two-hour PPG level from baseline to trial end was -1.4±3.8 mmol/L with acarbose compared to 1.1±3.5 mmol/L with placebo (P=0.0001).<br><br>Mean changes between acarbose compared to placebo for TG, fasting and postprandial serum insulin were not significant (P value not significant). |
| Phillips et al.[50] (2003)<br><br>Metformin (usual dose) and acarbose 50 mg to 100 mg BID<br><br>vs<br><br>metformin (usual dose) | DB, MC, PC, PG, RCT<br><br>Patients ≥40 years of age with type 2 diabetes for ≥6 months, BMI 25 to 35 kg/m$^2$, $HbA_{1c}$ 7.0 to 10.0% at screening week and 6.8 to 10.2% at baseline, and inadequately controlled by metformin | N=83<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG | Primary:<br>Mean $HbA_{1c}$ increased with placebo from 7.82±0.83% at baseline to 8.10±1.06% at week 12 and 8.50±1.44% at trial end. The mean increase after 24 weeks was 0.68±1.17%, with a significant overall time effect (P=0.0001).<br><br>With acarbose, mean $HbA_{1c}$ decreased from 8.02±0.85% at baseline to 7.78±1.00% at week 12 (P=0.0261). At the trial end, mean $HbA_{1c}$ increased to 7.97±1.10%. There was no significant overall time effect for acarbose (P value not reported).<br><br>Adjusted least square means for the change in $HbA_{1c}$ from baseline to trial end showed a decrease of 0.16±0.18% with acarbose compared to an increase of 0.86±0.16% with placebo. There was a significant difference between the treatment groups of 1.02% (95% CI, 0.543 to 1.497; P=0.0001).<br><br>Secondary:<br>Mean FPG levels increased with placebo from baseline (9.41 ±1.99 mmol/L) to week 4 (10.06 ±2.43 mmol/L) to trial end (10.77 ±3.39 mmol/L). The levels only changed slightly with acarbose.<br><br>Mean FPG increases were 1.36±2.88 mmol/L with placebo and 0.08±1.98 mmol/L with acarbose. The adjusted least square means showed increase at trial end with both treatments of 0.34±0.42 mmol/L with acarbose vs 1.48±0.39 mmol/L with placebo, with a significance of 1.132 mmol/L between the two treatments (95% CI, 0.056 to 2.208; P=0.0395). |
| Lopez-Alvarenga et al.[51] | DB, RCT, XO | N=46 | Primary:<br>Change in FPG | Primary:<br>Changes in FPG from baseline were not significant for placebo (P=0.62), |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (1999)<br><br>Metformin 1,200 mg daily, chlorpropamide 500 mg daily, and acarbose 100 mg TID<br><br>vs<br><br>metformin 1,200 mg daily, chlorpropamide 500 mg daily, and NPH insulin at bedtime<br><br>vs<br><br>metformin 1,200 mg daily, chlorpropamide 500 mg daily, and placebo | Patients with type 2 diabetes from 35 to 70 years of age with BMI 23 to 35 kg/m$^2$, with a FPG >8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months | 42 weeks | from baseline, body weight, $HbA_{1c}$, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area)<br><br>Secondary:<br>Not reported | but were significant for acarbose (P=0.05) and insulin (P=0.003).<br><br>Changes in $HbA_{1c}$ from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008).<br><br>Changes in body weight were not significant in any group (P=0.2 vs baseline).<br><br>Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02).<br><br>Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24).<br><br>Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94).<br><br>Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02).<br><br>Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43).<br><br>Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin.<br><br>Secondary:<br>Not reported |
| Haak et al.[52] (2012)<br><br>Linagliptin 5 mg QD | DB, MC, PC, RCT<br><br>Patients 18 to 80 years of age with type 2 diabetes who were treatment- | N=791<br><br>24 weeks | Primary:<br>Change from baseline in $HbA_{1c}$ at week 24<br><br>Secondary: | Primary:<br>After 24 weeks, the mean change in $HbA_{1c}$ was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin plus metformin 500 mg, and -1.6% with linagliptin plus metformin 1,000 mg. |

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| vs<br><br>metformin 500 mg BID<br><br>vs<br><br>metformin 1,000 mg BID<br><br>vs<br><br>linagliptin 2.5 mg BID and metformin 500 mg BID<br><br>vs<br><br>linagliptin 2.5 mg BID and metformin 1,000 mg BID<br><br>vs<br><br>placebo | naïve ($HbA_{1c}$ 7.5 to 11.0%) or who had received one other oral antidiabetic drug ($HbA_{1c}$ 7.0 to 10.5%) | | Change from baseline in FPG, change from baseline in $HbA_{1c}$ and FPG over time, proportion of patients requiring rescue therapy after failing to achieve pre-specified glycemic targets or discontinuing because of lack of efficacy, safety | The adjusted placebo-corrected mean changes in $HbA_{1c}$ were -1.7% (95% CI, -2.0 to -1.4) for linagliptin plus metformin 1,000 mg; -1.3% (95% CI, -1.6 to -1.1) for linagliptin plus metformin 500 mg; -1.2% (95% CI, -1.5 to -0.9) for metformin 1,000 mg; -0.8% (95% CI, -1.0 to -0.5) for metformin 500 mg, and -0.6% (95% CI, -0.9 to -0.3) for linagliptin monotherapy (*P*<0.0001 for all).<br><br>The mean treatment differences for linagliptin plus metformin 1,000 mg vs metformin and linagliptin monotherapy were -0.5% (95% CI, -0.7 to -0.3) and -1.1% (95% CI, -1.4 to -0.9), respectively. For linagliptin plus metformin 500 mg, the respective mean differences were -0.6% (95% CI, -0.8 to -0.4) and -0.8% (95% CI, -1.0 to -0.6; *P*<0.0001 for all).<br><br>Secondary:<br>The adjusted placebo-corrected mean changes in FPG from baseline were -3.3 mmol/L (95% CI, -4.0 to -2.6) and -2.4 mmol/L (95% CI, -3.1 to -1.7) in the linagliptin plus metformin 1,000 mg and linagliptin plus metformin 500 mg groups, respectively. This is compared to -2.3 mmol/L (95% CI, -3.0 to -1.7), -1.4 mmol/L (95% CI, -2.1 to -0.8) and -1.0 mmol/L (95% CI, -1.7 to -0.3) in the metformin 1,000 mg, metformin 500 mg, and linagliptin monotherapy groups, respectively (*P*<0.0001 for all).<br><br>The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin plus metformin 1,000 mg, 4.3%; linagliptin plus metformin 500 mg, 7.3%) compared to either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%).<br><br>The proportion of patients reporting adverse events were comparable across the active treatment groups. |
| Standl et al.[53] (2001)<br><br>Metformin 500 to 850 mg daily, miglitol 25 mg to 100 mg TID, and | DB, MC, PC, PG, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes for ≥3 years; $HbA_{1c}$ | N=154<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, PPG, fasting and postprandial | Primary:<br>Miglitol produced a significant reduction in $HbA_{1c}$ (-0.55%; P=0.04) and PPG (-2.6 mmol/L; P=0.0009) compared to placebo.<br><br>Secondary:<br>FPG decreased with miglitol and was almost unchanged with placebo; the difference was not significant (P=0.10). |

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| glibenclamide* 3.5 to 5 mg BID to QID<br><br>vs<br><br>metformin 500 to 850 mg daily and glibenclamide* 3.5 to 5 mg BID to QID | ≥7.5 to ≤10.5%; BMI ≤35 kg/m$^2$; stable body weight over the previous 3 months; and inadequately controlled on combination therapy of diet, glibenclamide* and metformin | | serum insulin, TG, urinary glucose | Fasting insulin levels were unchanged with both treatments throughout the trial, with no significant difference between them (P=0.79).<br><br>Postprandial insulin decreased from baseline to trial end, but the difference between the groups was not significant (P=0.26).<br><br>Postprandial TG decreased slightly with miglitol and remained unchanged with placebo, and the difference was not significant (P=0.47). |
| Van Gaal et al.[54] (2001)<br><br>Metformin 500 mg TID or 850 mg BID to TID and miglitol 25 to 100 mg TID<br><br>vs<br><br>metformin 500 mg TID or 850 mg BID to TID | DB, MC, PC, PG, RCT<br><br>Patients 30 to 75 years of age with type 2 diabetes for ≥1 year, $HbA_{1c}$ ≥7.5 to ≤10.5%, BMI 23 to 40 kg/m$^2$, stable body weight over the previous 3 months, and whose diabetes was inadequately controlled by diet and metformin | N=152<br><br>32 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in FPG, PPG, serum insulin, fasting and one-hour postprandial TG levels | Primary:<br>There was a significant decrease in $HbA_{1c}$ with miglitol compared to placebo (-0.21 vs 0.22%; P=0.011).<br><br>Secondary:<br>PPG decreased with both treatments, but the reduction was more significant with miglitol (from 16.5±3.8 mmol/L at baseline to 13.8±5.0 mmol/L at trial end) compared to placebo (from 16.3±3.4 mmol/L at baseline to 15.7±3.8 mmol/L at trial end). The baseline adjusted means were 13.8 mmol/L with miglitol vs 15.8 mmol/L with placebo (P=0.0007).<br><br>Fasting insulin levels decreased more with miglitol compared to placebo, the difference was not significant (P value not reported).<br><br>FPG, fasting and postprandial TG levels showed a descriptive advantage for miglitol, but did not reach a statistical difference. Mean FPG levels fell more with miglitol (baseline, 11.5±2.7 mmol/L; end of treatment, 10.8±3.6 mmol/L) compared to placebo (baseline, 11.6±3.1 mmol/L; end of treatment, 11.5±3.4 mmol/L; difference of adjusted means; P=0.15). Fasting TG levels fell with miglitol (treatment effect, -16.3 mg/dL) compared to placebo (treatment effect, 3.77 mg/dL; P=0.26). Similar results were seen for postprandial TG. |
| Chiasson et al.[55] (2001)<br><br>Metformin 500 mg | DB, MC, PC, RCT<br><br>Patients >40 years of age with type 2 | N=324<br><br>36 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>Mean change in $HbA_{1c}$ from baseline was 0.38±0.12% with placebo, 0.02±0.10% with miglitol, -0.85±0.12% with metformin, and -1.39±0.11% with combination therapy. A reduction in mean placebo-subtracted $HbA_{1c}$ |

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| TID and miglitol 100 mg TID<br><br>vs<br><br>metformin 500 mg TID<br><br>vs<br><br>miglitol 100 mg TID<br><br>vs<br><br>placebo | diabetes inadequately controlled by diet alone, $HbA_{1c}$ 7.2 to 9.5% | | Secondary:<br>Change in baseline FPG and PPG, insulin levels, and TG | of -1.78% was seen with combination therapy, and this was significantly different from metformin (-1.25%; P=0.002).<br><br>Mean reductions in $HbA_{1c}$ compared to placebo were -0.37% with miglitol, -1.25% with metformin, and -1.78% with combination therapy. The end of treatment mean $HbA_{1c}$ was 8.5% with placebo, 8.2% with miglitol, 7.3% with metformin, and 6.9% with combination therapy. Significantly more patients (P=0.0014) receiving combination therapy (70.6%) were classified as responders (i.e., showed ≥15% reduction from baseline in $HbA_{1c}$ or achieved an $HbA_{1c}$ <7.0%) compared to metformin (45.5%).<br><br>Secondary:<br>Combination therapy resulted in better metabolic control compared to metformin for FPG (P=0.0025) and two-hour PPG AUC (P=0.0001).<br><br>Changes in TG levels from baseline to trial end did not differ significantly between combination therapy compared to metformin, and showed no consistent trend (P value not reported). |
| DeFronzo et al.[56] (2009)<br><br>Metformin (existing therapy) and saxagliptin 2.5, 5, or 10 mg QD<br><br>vs<br><br>metformin (existing therapy) and placebo | DB, PC, RCT<br><br>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.0 to ≤10.0%), receiving stable doses of metformin (≥1,500 to <2,550 mg/day) ≥8 weeks, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | N=743<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an $HbA_{1c}$<7.0% | Primary:<br>Saxagliptin significantly decreased $HbA_{1c}$ compared to placebo (-0.59, -0.69, and -0.58 vs 0.13%; P<0.0001 for all), with significance achieved after four weeks.<br><br>Secondary:<br>Saxagliptin significantly decreased FPG compared to placebo (-14.31, -22.03, and -20.50 vs 1.24 mg/dL; P<0.0001 for all). Similar results were observed with PPG $AUC_{0\text{-}3hr}$ (-8,891, -9,586, and -8,137 vs -3,291 [mg/minute]/[dL]; P<0.0001 for all).<br><br>A significantly greater proportion of patients achieved an $HbA_{1c}$ <7.0% with saxagliptin compared to placebo (37.1, 43.5, and 44.4 vs 16.6%; P<0.0001 for all). |
| Pfutzner et al.[57] (2011) | AC, DB, ES, MC, RCT | N=1,306 | Primary:<br>Change in baseline | Primary:<br>Decreases in $HbA_{1c}$ with saxagliptin 5 mg plus metformin were -2.31% |

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| Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day<br><br>vs<br><br>saxagliptin 10 mg QD<br><br>vs<br><br>metformin 500 mg/day | Type 2 diabetics 18 to 77 years of age, $HbA_{1c}$ ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | 52 weeks (76 weeks total) | $HbA_{1c}$<br><br>Secondary:<br>Change in baseline body weight, proportion of patients achieving an $HbA_{1c}$ <7.0 and ≤6.5% | (95% CI -2.44 to -2.18) and -2.33% (95% CI -2.46 to -2.20) with saxagliptin 10 mg plus metformin compared to -1.55 (95% CI, -1.70 to -1.40) and -1.79% (95% CI, -1.93 to -1.65) with saxagliptin and metformin monotherapies, respectively; P<0.0001 for combination therapy vs monotherapy).<br><br>Secondary:<br>Decreases in body weight were -1.2 kg with saxagliptin 5 mg plus metformin, -0.7 kg with saxagliptin 10 mg plus metformin, -0.3 kg with saxagliptin, and -1.0 kg with metformin (P values not reported).<br><br>A greater proportion of patients achieved an $HbA_{1c}$ <7.0% with saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin compared to saxagliptin and metformin (51.5 and 50.5 vs 25.0 and 34.7%, respectively; P values not reported). Similar results were observed with $HbA_{1c}$ <6.5% (P values not reported). |
| Jadzinsky et al.[58] (2009)<br><br>Metformin 500 to 2,000 mg daily and saxagliptin 5 mg QD<br><br>vs<br><br>metformin 500 to 2,000 mg daily and saxagliptin 10 mg QD<br><br>vs<br><br>metformin 500 to 2,000 mg daily<br><br>vs | AC, DB, MC, RCT<br><br>Type 2 diabetics 18 to 77 years of age, $HbA_{1c}$ ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | N=1,306<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an $HbA_{1c}$ <7.0 and ≤6.5%, proportion of patients requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks | Primary:<br>Combination therapy significantly decreased $HbA_{1c}$ compared to monotherapy with either saxagliptin or metformin (-2.5 and -2.5 vs -1.7 and -2.0%, respectively; *P*<0.0001 vs monotherapy for all).<br><br>Secondary:<br>Combination therapy significantly decreased FPG compared to monotherapy with either saxagliptin or metformin (*P*=0.0002 for saxagliptin 5 mg plus metformin vs saxagliptin and *P*<0.001 for saxagliptin 10 mg plus metformin vs saxagliptin and metformin). Similar results were observed for PPG $AUC_{0\text{-}3hr}$ (*P*<0.0001 for all vs monotherapy).<br><br>The proportion of patients achieving an $HbA_{1c}$ <7.0% was significantly greater with combination therapy compared to monotherapy with either agent (60.3 and 59.7 vs 32.2 and 41.1%; *P*<0.0001 for all vs monotherapy). Similar results were observed for $HbA_{1c}$ ≤6.5% (45.3 and 40.6 vs 20.3 and 29.0%; *P*<0.0001 for saxagliptin 5 mg plus metformin vs saxagliptin and metformin; *P*<0.0001 for saxagliptin 10 mg plus metformin vs saxagliptin, and *P*=0.0026 for saxagliptin 10 mg plus metformin vs metformin). |

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| saxagliptin 10 mg QD | | | | At week 24, 7.5% of patients receiving saxagliptin 5 mg plus metformin and 21.2% of patients receiving saxagliptin 10 mg were discontinued or rescued for lack of glycemic control (*P*<0.0001). No significance was observed when saxagliptin 5 mg plus metformin was compared to metformin (*P*=0.2693). Similar results were observed with saxagliptin 10 mg plus metformin compared to either monotherapy (*P*<0.0001 vs saxagliptin 10 mg and *P*=0.0597 vs metformin). |
| Derosa et al.[59] (2010)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>metformin 850 mg BID<br><br>All patients were receiving pioglitazone (15 or 30 mg/day). | DB, RCT<br><br>Patients with type 2 diabetes, $HbA_{1c}$ >7.5%, and receiving pioglitazone 30 mg/day | N=151<br><br>12 months | Primary:<br>Body weight, BMI, $HbA_{1c}$, FPG, PPG, fasting plasma insulin, HOMA-IR, HOMA-B, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, adiponectin, resistin, TNF-α, high sensitivity CRP<br><br>Secondary:<br>Not reported | Primary:<br>A decrease in body weight and BMI were observed in patients receiving metformin, which was not observed in patients receiving sitagliptin.<br><br>Significant decreases in $HbA_{1c}$, FPG, and PPG, and significant increases in HOMA-B were comparable between the two treatment groups.<br><br>Fasting plasma insulin, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, and HOMA-IR were decreased with both treatments. While values were lower with metformin, there were no significant differences observed between the two treatments.<br><br>Sitagliptin achieved no significant changes in changes in adiponectin, resistin, TNF-α, compared to a significant increase in adiponectin and significant decreases in resistin and TNF-α achieved with metformin.<br><br>High sensitivity CRP decreased significantly with both treatments, with no difference between them.<br><br>Secondary:<br>Not reported |
| Goldstein et al.[60] (2007)<br><br>Sitagliptin 50 mg BID plus metformin 500 and 1,000 mg BID | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 78 years of age and an $HbA_{1c}$ of 7.5 to 11.0% | N=1,091<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, fasting serum insulin, fasting | Primary:<br>Decreases in $HbA_{1c}$ were significant with all active treatments as compared to placebo and for combination therapy compared to monotherapy (P<0.001). There was an additive effect seen in the combination treatment groups. The proportion of patients achieving an $HbA_{1c}$ <7.0% was significantly greater with all active treatments compared to placebo (P<0.001). |

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| vs<br><br>sitagliptin 100 mg QD<br><br>vs<br><br>metformin 500 and 1,000 mg BID<br><br>vs<br><br>placebo | | | serum proinsulin, lipid profiles, β cell function, insulin resistance; adverse events | Secondary:<br>Significant decreases in FPG were achieved between combination therapy and monotherapy, and between all active treatments compared to placebo (P<0.001).<br><br>Data on fasting serum insulin and lipid profiles were not reported.<br><br>Combination therapy demonstrated an additive effect, as compared to monotherapy, with regards to improvements in β cell function.<br><br>HOMA-B increased with all active treatments compared to placebo (P<0.001). The combination therapy significantly increased HOMA-B compared to monotherapy (sitagliptin and low-dose metformin; P≤0.001).<br><br>Significant improvements in the proinsulin:insulin ratio observed with all active treatments compared to placebo (P<0.05). Differences between combination therapy and monotherapy were also significant (P<0.05).<br><br>The incidence of adverse events was similar between combination therapy and metformin. Gastrointestinal adverse events including diarrhea, nausea, abdominal pain, and vomiting were most frequently observed with metformin high-dose both as monotherapy and combination therapy. A low frequency of hypoglycemia was similar among all treatments (0.6 to 2.2%). No change in weight was observed with sitagliptin compared to all other active treatments, where there was a significant decrease in body weight (-0.6 to -1.3 kg; P<0.05) and placebo (-0.9 kg; P<0.01). |
| Reasner et al.[61] (2011)<br><br>Sitagliptin/ metformin 50/500 to 1,00 mg BID<br><br>vs<br><br>metformin 500 to 1,000 mg BID | DB, MC, PG, RCT<br><br>Treatment-naïve type 2 diabetics 18 to 78 years of age, and an $HbA_{1c}$ ≥7.5% | N=1,250<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving an $HbA_{1c}$ <7.0 and <6.5%, change in baseline FPG, proinsulin:insulin | Primary:<br>Combination therapy significantly decreased $HbA_{1c}$ compared to metformin (-2.4 vs -1.8%; P<0.001).<br><br>Secondary:<br>A significantly greater proportion of patients receiving combination therapy achieved an $HbA_{1c}$ <7.0% (49.2 vs 34.2%, respectively; P<0.001) and <6.5% (31.8 vs 16.0%, respectively; P<0.001) compared to patients receiving metformin.<br><br>Combination therapy significantly decreased FPG compared to metformin |

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| | | | ratio, and β cell function | (-3.8 vs -3.0 mg/dL; P<0.001).<br><br>Combination therapy significantly decreased proinsulin:insulin ratio compared to metformin (-0.238 vs -0.186; P<0.05).<br><br>Combination therapy significantly improved β cell function compared to metformin (P<0.05). |
| Raz et al.[62] (2008)<br><br>Metformin 1,500 to 2,550 mg daily and sitagliptin 100 mg daily<br><br>vs<br><br>metformin 1,500 to 2,550 mg daily and placebo | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 78 years of age, $HbA_{1c}$ 7.0 to 10.0% receiving metformin or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents | N=190<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$ at 18 weeks<br><br>Secondary:<br>Change in baseline FPG at 18 weeks, two-hour PPG at 18 weeks, and $HbA_{1c}$ at 30 weeks; safety and tolerability | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo (treatment difference, -1.0%; 95% CI, -1.4 to -0.7; P<0.001). Numerically greater decreases in $HbA_{1c}$ were observed in patients with a higher baseline $HbA_{1c}$. A greater proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% at weeks 18 and 30 compared to patients receiving placebo (13.7 and 22.1 vs 3.3 and 3.3%; P values not reported).<br><br>Secondary:<br>Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -1.4 mmol/L; 95% CI, -2.1 to -0.7; P<0.001).<br><br>Sitagliptin significantly decreased two-hour PPG compared to placebo (treatment difference, -3.0 mmol/L; 95% CI, -4.2 to -1.9; P<0.001).<br><br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo at week 30 (treatment difference, -1.0%; 95% CI, -1.4 to -0.6; P<0.001).<br><br>The incidence of adverse events was similar with both treatments. No serious adverse events or discontinuations due to clinical adverse events were reported with sitagliptin. With placebo, there were six serious clinical adverse events that resulted in one death and two discontinuations. None of the adverse events were deemed to be drug-related. There were no differences between the two treatments in the incidences of hypoglycemia or gastrointestinal adverse events (abdominal pain, nausea, vomiting, and diarrhea). Over the 30 week period a small decrease in weight of 0.5 kg was observed with both treatments. |
| Perez-Monteverde et al.[63] (2011) | DB, RCT<br><br>Patients with type 2 | N=492 (Phase 1) | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>At the end of Phase 1 (12 weeks), mean changes from baseline in $HbA_{1c}$ were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase |

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| Sitagliptin/ metformin<br><br>vs<br><br>pioglitazone 30 to 45 mg QD<br><br>In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD.<br><br>In Phase 2, patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/ metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day. | diabetes and $HbA_{1c}$ 7.5 to 12.0% | 12 weeks (Phase 1) plus 28 weeks (Phase 2) | Secondary:<br>Change in baseline FPG and 2-hour PPG, proportion of patients achieving $HbA_{1c}$ <7.0%, safety, body weight | 2 (40 weeks), improvements in $HbA_{1c}$ were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; P=0.002).<br><br>Secondary:<br>At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for two-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and two-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001).<br><br>Significantly more patients receiving combination therapy achieved an $HbA_{1c}$ <7.0% (55.0 vs 40.5%; P=0.004).<br><br>A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of oedema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments.<br><br>Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001). |
| Wainstein et al.[64] (2012)<br><br>Sitagliptin/ metformin 50/500 mg BID, titrated up to 50/1,000 mg BID | DB, RCT<br><br>Treatment-naïve patients with type 2 diabetes $HbA_{1c}$ 7.5 to 12.0% | N=517<br><br>32 weeks | Primary:<br>Change from baseline $HbA_{1c}$, proportion of patients who achieved $HbA_{1c}$ <7.0%<br><br>Secondary: | Primary:<br>The least squares mean changes in $HbA_{1c}$ at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001).<br><br>A greater proportion of patients achieved an $HbA_{1c}$ <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001).<br><br>Secondary: |

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| vs<br><br>pioglitazone 30 mg/day, titrated up to 45 mg/day | | | Change from baseline FPG | Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone.<br><br>A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy.<br><br>Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001).<br><br>Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of oedema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone.<br><br>There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055). |
| Scott et al.[65] (2008)<br><br>Metformin (existing therapy) and sitagliptin 100 mg QD<br><br>vs<br><br>metformin (existing therapy) and rosiglitazone 8 mg QD | AC, DB, MC, PG, RCT<br><br>Type 2 diabetics 18 to 75 years of age receiving stable metformin doses (≥1,500 mg/day for ≥10 weeks) and inadequate glycemic control ($HbA_{1c}$ ≥7.0 and ≤11.0%) | N=273<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; P≤0.001). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14).<br><br>The proportion of patients achieving an $HbA_{1c}$<7.0% was significantly greater with sitagliptin (55%; P=0.006) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported).<br><br>Secondary: |

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| vs<br><br>metformin and placebo | | | | Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; P≤0.001) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo.<br><br>Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported).<br><br>Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; P≤0.05) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported).<br><br>Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).<br><br>Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 µIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 µIU/mL; 95% CI, -5.50 to -1.40; P value not reported).<br><br>The proinsulin:insulin ratio was similar across all treatments.<br><br>Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; P≤0.05) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin |

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| | | | | (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; P≤0.05) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported). |
| Hermansen et al.[66] (2007)<br><br>Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily<br><br>vs<br><br>sitagliptin 100 mg QD plus glimepiride 4 to 8 mg daily<br><br>vs<br><br>glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo<br><br>vs<br><br>glimepiride 4 to 8 mg daily plus placebo | DB, DD, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 75 years of age, $HbA_{1c}$ 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin | N=441<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ (P<0.001) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in $HbA_{1c}$ compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32).<br><br>A significantly greater proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (17.1 vs 4.8%; P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an $HbA_{1c}$ <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638).<br><br>Secondary:<br>Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001).<br><br>Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported).<br><br>A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and quantitative insulin sensitivity check index between the treatments.<br><br>Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; P<0.001). |

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| | | | | Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia.<br>A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1). |
| Rigby et al.[67] (2010)<br><br>Rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy)<br><br>vs<br><br>sitagliptin 100 mg QD and metformin (existing therapy)<br><br>vs<br><br>colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy) | OL<br><br>Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control ($HbA_{1c}$ 6.5% to 10.0% on a stable regimen of metformin (1,500-2,550 mg daily), with LDL-C ≥60 mg/dL and TGs <500 mg/dL | N=169<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to week 16<br><br>Secondary:<br>Change in $HbA_{1c}$ from baseline to week 8, change in FPG and fasting insulin from baseline to weeks 8 and 16, change in 2-hour PPG and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an $HbA_{1c}$ reduction >0.7% from baseline, percentage of participants who achieved $HbA_{1c}$ <7.0% | Primary:<br>At week 16, $HbA_{1c}$ was reduced from baseline in all treatment groups (LS mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009).<br><br>Secondary:<br>At week 8, $HbA_{1c}$ was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109).<br><br>FPG was significantly reduced from baseline at week 8 and week 16 in all treatment groups.<br><br>The 2-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups.<br><br>There was no significant change in fasting insulin or 2-hour postprandial insulin from baseline to week 16 in any treatment group.<br><br>Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008).<br><br>LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011).<br><br>TC levels were unchanged from baseline with colesevelam and sitagliptin; |

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| | | | | however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median TG levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment.<br><br>At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in $HbA_{1c}$ of 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved $HbA_{1c}$ <7.0%.<br><br>The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity. |
| Douek et al.[68] (2005)<br><br>Metformin titrated to 2 grams daily<br><br>vs<br><br>placebo<br><br>All patients received insulin regimens. | DB, MC, PC, RCT<br><br>Patients ≤75 years of age with type 2 diabetes for ≥2 years starting insulin due to inadequate glycemic control on oral agents | N=183<br><br>1 year | Primary:<br>Change in baseline weight<br><br>Secondary:<br>Changes in baseline $HbA_{1c}$, insulin dose, frequency of hypoglycemia, treatment satisfaction, well-being from baseline | Primary:<br>Metformin was associated with less weight gain than placebo (mean, 6.1 vs 7.6 kg; adjusted difference, 1.5 kg; 95% CI, 0.2 to 2.9; P=0.02).<br><br>Secondary:<br>Metformin was associated with a greater decrease in $HbA_{1c}$ (1.5 vs 1.3%; adjusted difference, 0.5%; 95% CI, 0.1 to 0.9%; P=0.02), and a lower insulin requirement (62 vs 86 units; adjusted difference, 25 units; 95% CI, 15 to 34; P<0.001) compared to placebo.<br><br>Severe hypoglycemia was reported in 10 patients (13%) taking metformin and in one patient (1%) taking placebo (RR, 9.48; 95% CI, 1.24 to 72.2; P=0.009).<br><br>Treatment satisfaction improved more in patients on metformin than on placebo (P<0.001) as did the positive-well-being score (P=0.02). |
| Wulffelé et al.[69] (2002) | DB, PC, RCT | N=390 | Primary:<br>Changes in $HbA_{1c}$, | Primary:<br>Mean $HbA_{1c}$ was 6.94% for metformin and 7.6% for placebo (P<0.0001). |

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| Metformin 850 to 2,250 mg daily<br><br>vs<br><br>placebo<br><br>All patients received insulin regimens. | Patients 30 to 80 years of age with type 2 diabetes who had received a diagnosis of diabetes after the age of 25, who had experienced no episodes of ketoacidosis, and whose past blood-glucose lowering treatments consisted of oral agents but now consisted of insulin or a combination of insulin and metformin | 16 weeks interim analysis | insulin requirements, body weight, BMI, BP, and plasma lipids<br><br>Secondary:<br>Not reported | Mean daily glucose level decreased from 8.8±2.1 to 8.5±1.7 mmol/L in the placebo group (mean decrease, -0.16; 95% CI, -0.53 to 0.22 mmol/L) and from 8.8±2.2 to 7.8±1.7 mmol/L in the metformin group (mean decrease, -1.04; 95% CI, -1.5 to 0.52 mmol/L; P=0.006 vs placebo).<br><br>Mean insulin requirements were significantly different for metformin (63.8 IU) as compared to placebo (71.3 IU; P<0.0001).<br><br>Mean weight reduction was significant for metformin (-0.4 kg) as compared to placebo (1.2 kg; P<0.01). BMI increased by 0.4±2 kg in the placebo group and decreased by 0.2±0.9 kg in the metformin group (P=0.01 vs placebo).<br><br>There was a small increase in mean SBP and DBP in both groups, but the difference was not significant between the groups (P=0.87 for SBP and P=0.92 for DBP).<br><br>In the placebo group, mean plasma TC and LDL-C concentrations decreased by -0.04 mmol/L (95% CI, -0.15 to 0.07) and -0.02 mmol/L (95% CI, -0.16 to 0.06), respectively. In the metformin group, mean plasma TC and LDL-C concentrations decreased by -0.25 mmol/L (95% CI, -0.35 to -0.15) and -0.21 mmol/L (95% CI, -0.33 to -0.15), respectively (P<0.01 vs placebo for both).<br><br>Changes in plasma HDL-C and TG concentrations were not significant in either group.<br><br>Mild and transient gastrointestinal complaints were reported more frequently in the metformin group (56%) as compared to the placebo group (13%; P<0.0001).<br><br>Secondary:<br>Not reported |
| Yki-Järvinen et al.[70]<br>(2006) | MC, OL, PG, RCT | N=110<br><br>36 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline | Primary:<br>At 36 weeks, $HbA_{1c}$ decreased from 9.13±0.15% to 7.14±0.12% and from 9.26±0.15% to 7.16±0.14% in the G+MET and NPH+MET groups, |

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| Bedtime insulin glargine plus metformin (G+MET)<br><br>vs<br><br>bedtime NPH plus metformin (NPH+MET)<br><br>Initial bedtime doses were 10 units for patients who were previously on metformin alone and 20 units for patients who were previously on both metformin and a sulfonylurea.<br><br>All sulfonylurea medications were discontinued according to the study protocol.<br><br>Insulin doses were titrated to achieve an FPG 72 to 100 mg/dL in both groups. | Men and women 35 to 75 years of age with type 2 diabetes previously treated with a stable dose of sulfonylurea and metformin (>1.5 g) or metformin alone for at least 3 months prior to screening, with a BMI 20 to 40 kg/m$^2$, $HbA_{1c}$ ≥8.0%, FPG ≥7 mmol/L measured during self monitoring of blood glucose between 4 and 2 weeks prior to study start, and fasting C-peptide ≥0.33 nmol/L | | Secondary:<br>Diurnal glucose concentrations, symptomatic hypoglycemia | respectively. The changes in $HbA_{1c}$ were determined to be not significant between groups (P value not reported).<br><br>Secondary:<br>The diurnal profiles were consistently lower in the G+MET group compared to the NPH+MET group (8.6±0.3 vs 10.1±0.3 mmol/L, respectively; P=0.002).<br><br>During the first 12 weeks, the G+MET group had significantly lower number of episodes of symptomatic hypoglycemia than the NPH+MET group, but the rates became similar thereafter. The frequency of hypoglycemia averaged 5.4 and 8.0 episodes/patient-year for the G+MET and NPH+MET groups, respectively (P=0.12). |
| Horton et al.[71] | DB, PC, PRO, RCT | N=701 | Primary: | Primary: |

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| (2000)<br><br>Nateglinide 120 mg TID before each meal plus metformin 500 mg TID immediately after the start of each meal<br><br>vs<br><br>nateglinide 120 mg TID before each meal<br><br>vs<br><br>metformin 500 mg TID immediately after the start of each meal<br><br>vs<br><br>placebo | Patients ≥30 years of age with type 2 diabetes for ≥3 months with a BMI 20 to 35 kg/m$^2$, and all patients needed to have been treated with diet alone with an $HbA_{1c}$ 6.8 to 11.0% and FPG level ≤15 mmol/L | 24 weeks | Change in $HbA_{1c}$, FPG, glucose AUC after Sustacal challenge from baseline<br><br>Secondary:<br>Not reported | Adjusted mean change from baseline in $HbA_{1c}$, FPG, and glucose AUC after Sustacal challenge were significantly reduced from baseline (P≤0.0001) in patients receiving active treatment.<br><br>$HbA_{1c}$, FPG, and glucose AUC were all significantly reduced compared to placebo (P≤0.001), except from glucose AUC with metformin monotherapy.<br><br>The decrease in $HbA_{1c}$ was greater for metformin compared to nateglinide, the between group difference was small (0.3% difference; P≤0.01).<br><br>The decrease in FPG was greater with the metformin group compared to the nateglinide group, the between group difference was 0.9 mmol/L (P<0.001).<br><br>The combination of nateglinide plus metformin was additive ($HbA_{1c}$, -1.4% and FPG, -2.4 mmol/L; P≤0.01 vs either monotherapy).<br><br>After a Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide compared to metformin or placebo ($AUC_{0\text{-}130\ min}$, -2.1, -1.1, and 0.6 mmol/hr/L, respectively; P≤0.0001). A greater reduction was seen with nateglinide plus metformin ($AUC_{0\text{-}130\ min}$, -2.5 mmol/hr/L; P≤0.0001 vs metformin and placebo).<br><br>Secondary:<br>Not reported |
| Marre et al.[72] (2002)<br><br>Metformin 1,000 mg BID and nateglinide 60 to 120 mg TID before meals<br><br>vs | DB, MC, PG, RCT<br><br>Patients ≥30 years of age with type 2 diabetes for ≥6 months with $HbA_{1c}$ 6.8 to 11.0%, BMI 20 to 35 kg/m$^2$, and were treated with metformin for a minimum of 3 | N=467<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change in FPG, body weight, and lipid profile (TC, fasting TGs, LDL-C, HDL-C) | Primary:<br>Mean $HbA_{1c}$ was reduced significantly from baseline when compared to the placebo group for the nateglinide 60 mg group (-0.36%; 95% CI, -0.59 to -0.13; P=0.003) and for the nateglinide 120 mg group (-0.51%; 95% CI, -0.82 to -0.36; P<0.001) at end point.<br><br>Dose-dependent reduction in $HbA_{1c}$ was seen with nateglinide irrespective of baseline parameters, with larger mean reductions seen with nateglinide 120 mg. There was little or no change in $HbA_{1c}$ at end point in the placebo group. |

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| metformin 1,000 mg BID and placebo | months and stabilized at a dose of ≥1,500 mg/day for ≥4 weeks prior to study entry | | | Secondary:<br>There were modest changes from baseline in FPG in the nateglinide groups and an increase was seen in the placebo group, the difference compared to baseline was significant in both the nateglinide 60 and 120 mg groups (P=0.044 and P=0.003, respectively).<br><br>There were no notable changes in body weight at end point in the patients that received placebo (0.1 kg) or nateglinide 60 mg (0.4 kg). There was a significant increase (P<0.001) in mean weight of 0.9 kg in the nateglinide 120 mg group as compared to baseline.<br><br>Fasting TGs were significantly reduced in the nateglinide 120 mg group as compared to the placebo group at end point (P=0.042). The mean changes in TC, LDL-C, and HDL-C remained almost unchanged throughout the study. |
| Raskin et al.[73] (2003)<br><br>Metformin 1,000 mg BID and nateglinide 120 mg TID before meals<br><br>vs<br><br>metformin 1,000 mg BID and repaglinide 1 to 4 mg TID before meals | MC, OL, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m$^2$, $HbA_{1c}$ 7.0 to 12.0% on previous monotherapy with a sulfonylurea, metformin, or low dose glyburide plus metformin | N=192<br><br>16 weeks | Primary:<br>Final $HbA_{1c}$ values and changes in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Changes in FPG and assessment of glucose area under the time concentration curves from 0 to 240 minutes ($AUC_{0\text{-}240\ min}$), insulin $AUC_{0\text{-}240\ min}$, and glucagon $AUC_{0\text{-}240\ min}$ after a liquid test meal at baseline and at study end point | Primary:<br>Mean $HbA_{1c}$ changes from baseline were significantly greater in the repaglinide group compared to the nateglinide group (-1.28 vs -0.67%; P<0.001).<br><br>The final $HbA_{1c}$ at 16 weeks was 7.1±1.1% for the repaglinide group and 7.5±1.4% for the nateglinide group.<br><br>The percent of patients who achieved final $HbA_{1c}$ values ≤7.0% was 59% for the repaglinide group and 47% for the nateglinide group (P value not reported).<br><br>Secondary:<br>FPG values were significantly different between the two treatment groups with one week of therapy. Mean changes in FPG values from baseline were significantly greater for the repaglinide group (-39 vs -21 mg/dL for nateglinide group; P=0.002). The final FPG at 16 weeks was 150.0±45.1 mg/dL for the repaglinide group and 170±52 mg/dL for the nateglinide group. At the end of the 16 week maintenance study, 48% of the repaglinide group had reductions of FPG values >40 mg/dL and 26% of the nateglinide group had a response of this magnitude. |

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| | | | | Mean end point reductions in PPG levels from baseline were not significantly different between the groups (glucose $AUC_{0\text{-}240\ min}$). The treatments were also similar for changes in insulin $AUC_{0\text{-}240\ min}$ and glucagon $AUC_{0\text{-}240\ min}$ during the study (P values not reported).<br><br>There were no patients in either group who experienced major hypoglycemic episodes (requiring the assistance of another person).<br><br>The most frequent adverse event in both groups was upper respiratory infection (12 vs 21%). Adverse events that occurred from 3 to 8% included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide group had 5% incidence of chest pain and arthralgia, as compared to 1% for each in the nateglinide groups. Mean changes from baseline in weight were small for both groups, 0.6 kg gain for repaglinide compared to 0.5 kg loss with nateglinide. |
| Gerich et al.[74] (2003) PRESERVE-β Study<br><br>Metformin 500 to 2,000 mg daily plus nateglinide 120 mg TID<br><br>vs<br><br>metformin 500 to 2,000 mg daily plus glyburide 1.25 to 10 mg daily | DB, MC, RCT<br><br>Men and women 18 to 77 years of age with type 2 diabetes, drug naïve, $HbA_{1c}$ 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m$^2$ and inadequately controlled on diet and exercise | N=428<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline (average of weeks -2 and 0) to week 104<br><br>Secondary:<br>Change from baseline to week 104 in FPG, body weight, $AUC_{0\text{-}120\ min}$ of glucose during oral glucose tolerance tests | Primary:<br>Both treatments maintained similar reductions in $HbA_{1c}$. The mean change in $HbA_{1c}$ from baseline to week 104 in the nateglinide plus metformin group (-1.2±0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (-1.5±0.1%). The changes in $HbA_{1c}$ were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups.<br><br>Secondary:<br>Mean change in FPG was -1.6±0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and -2.4±0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).<br><br>Body weight decreased in the nateglinide plus metformin group (-0.4±0.4 kg) and increased in the glyburide plus metformin group (0.8±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115).<br><br>No data was reported for AUC of glucose during oral glucose tolerance |

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| | | | | tests. |
| Schwarz et al.[75] (2008)<br><br>Metformin 2,000 mg QD and nateglinide 120 mg TID before meals<br><br>vs<br><br>metformin 2,000 mg QD and glyburide 10 mg QD | AC, DB, MC, RCT<br><br>Men and women ≥65 years of age with type 2 diabetes, drug naïve, $HbA_{1c}$ 7.0 to 11.0%, FPG ≤15 mmol/L, BMI of 22 to 45 $kg/m^2$ | N=69<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change from baseline to week 104 in FPG, two-hour PPG using the incremental AUC ($AUC_{0\text{-}120\ min}$) of glucose during oral glucose tolerance tests, the proportion of patients achieving a target $HbA_{1c}$ <7.0 or ≤6.5%, adverse events | Primary:<br>Similar reductions in $HbA_{1c}$ were seen with both treatments. The average change in $HbA_{1c}$ from baseline to week 104 in the nateglinide plus metformin group (-1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (-1.2±0.1%). The changes in $HbA_{1c}$ were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups.<br><br>Secondary:<br>Mean change in FPG was -26±6 mg/dL in patients receiving nateglinide plus metformin (P<0.001 vs baseline) and -36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups).<br><br>There was no significant changes in two-hour PPG from baseline for nateglinide plus metformin glyburide plus metformin groups (-15±7 mg/dL; P=0.071 and -8±8 mg/dL; P=0.385, respectively).<br><br>The proportion of patients who achieved a target $HbA_{1c}$ <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736).<br><br>Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target $HbA_{1c}$ of ≤6.5% (40 and 60%, respectively; P=0.206).<br><br>Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs 8 mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023). |
| Derosa et al.[76] (2009)<br><br>Metformin 1,500 | DB, MC, PG, RCT<br><br>Patients ≥18 years of age with type 2 | N=248<br><br>12 months | Primary:<br>Changes in BMI, FPG and PPG, $HbA_{1c}$, fasting and | Primary:<br>BMI did not show any significant change during the study.<br><br>A significant reduction in $HbA_{1c}$ was shown after 9 months (P<0.05) and |

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| to 3,000 mg daily plus nateglinide 60 mg TID<br><br>vs<br><br>metformin 1,500 to 3,000 mg daily plus glyburide 7.5 to 12.5 mg daily | diabetes, $HbA_{1c}$ >7.0%, BMI 25 to 28 kg/m$^2$, and hypertensive (SBP/DBP, >130/≥85 mmHg) | | postprandial plasma insulin, HOMA index, and lipid profile, BP | 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in $HbA_{1c}$ was seen with glyburide after 12 months (P<0.05) compared to baseline. The $HbA_{1c}$ at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05).<br><br>After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline.<br><br>Significant changes in PPG were found at nine months (P<0.05) in the nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline.<br><br>Fasting plasma insulin and postprandial plasma insulin did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline.<br><br>HOMA index decrease was obtained only at 12 months (P<0.05) compared to the baseline value in both groups,<br><br>No significant change was observed in TC, LDL-C, HDL-C, TG, Apo A-I, Apo B, SBP, DBP and heart rate in either group after three, six, nine and 12 months. |
| Wang et al (abstract).[77] (2011)<br><br>Repaglinide 1 mg TID, titrated up to 4 mg TID<br><br>vs<br><br>repaglinide 1 mg TID plus metformin 500 mg | AC, OL, PG, RCT<br><br>Patients 18 to 75 years of age with type 2 diabetes, $HbA_{1c}$ >8.5%, BMI ≤35 kg/m$^2$, and who were naïve to oral antidiabetic agents, | N=432<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, two-hour PPG, seven-point plasma glucose, safety | Primary:<br>Mean $HbA_{1c}$ reduction was 4.51±1.64% with combination therapy and 4.05±1.59% with repaglinide. Estimated mean treatment difference for combination therapy vs repaglinide was -0.30% (95% CI, -0.49 to -0.11; P< 0.01).<br><br>Secondary:<br>Combination therapy demonstrated significant improvements compared to repaglinide in FPG, seven-point plasma glucose, and lunchtime and dinnertime two-hour PPG (P<0.05 for all).<br><br>Hypoglycemia rates were 2.04 events/patient-year with combination therapy compared to 1.35 events/patient-year with repaglinide (P=0.058). |

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| TID, titrated up to 4 mg TID and 500 mg TID | | | | Adverse events were comparable between the two treatments. |
| Moses et al.[78] (1999)<br><br>Repaglinide 0.5 to 4 mg TID before each meal plus metformin 1,000 to 3,000 mg/day<br><br>vs<br><br>repaglinide 0.5 to 4 mg TID before each meal<br><br>vs<br><br>metformin 1,000 to 3,000 mg/day | DB, MC, PG, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes treated with metformin alone (1 to 3 g/day) for >6 months and had not achieved optimal glycemic control ($HbA_{1c}$ >7.0%) and BMI ≥21 kg/m$^2$ | N=83<br><br>3 months | Primary:<br>Change in baseline $HbA_{1c}$ and FPG<br><br>Secondary:<br>Change in fasting insulin, C-peptide levels, fasting TG, TC, HDL-C, LDL-C, FFA, body weight | Primary:<br>Patients in the metformin plus repaglinide group had a significant decrease in $HbA_{1c}$ from 8.3 to 6.9% (P=0.0016) and FPG from 10.2 to 8.0 mmol/L (P=0.0003) compared to baseline. There were no significant changes in $HbA_{1c}$ or FPG for patients receiving metformin alone and repaglinide alone. The $HbA_{1c}$ and FPG changes from baseline for metformin plus repaglinide vs metformin alone and metformin plus repaglinide vs repaglinide were significant (P<0.05 for all).<br><br>Secondary:<br>Fasting insulin and C-peptide levels increased significantly from baseline in both groups receiving repaglinide (P<0.05 for both).<br><br>Lipid levels (TC, HDL-C, LDL-C, TG, FFA) did not change significantly from baseline in the metformin plus repaglinide group. No significant differences were found between the metformin plus repaglinide group and the monotherapy groups.<br><br>In both groups receiving repaglinide there was an increase in body weight which was significant compared to baseline (P<0.05 for both). |
| Civera et al.[79] (2008)<br><br>Metformin 850 mg BID, repaglinide 2 mg TID before meals, and NPH insulin before dinner<br><br>vs<br><br>metformin 850 mg BID and NPH | OL, PG<br><br>Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs | N=37<br><br>24 weeks | Primary:<br>$HbA_{1c}$, hypoglycemia, body weight<br><br>Secondary:<br>Not reported | Primary:<br>The $HbA_{1c}$ was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02).<br><br>The absolute reduction in $HbA_{1c}$ was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group.<br><br>Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01).<br><br>Significant differences in weight gain and hypoglycemia were not seen. |

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| insulin before dinner<br><br>vs<br><br>NPH insulin BID | | | | Secondary:<br>Not reported |
| Black et al.[80] (2007)<br><br>Meglitinide<br><br>vs<br><br>meglitinide plus metformin<br><br>vs<br><br>meglitinide plus insulin<br><br>vs<br><br>metformin<br><br>vs<br><br>placebo | MA (15 trials)<br><br>Patients with type 2 diabetes | N=3,781<br><br>Duration varied | Primary:<br>Mortality and morbidity<br><br>Secondary:<br>Change in $HbA_{1c}$, weight or BMI, hypoglycemia, adverse effects, quality of life | Primary:<br>No trials reported the effect of meglitinides on mortality and morbidity.<br><br>Secondary:<br>In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in $HbA_{1c}$ (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in $HbA_{1c}$ was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in $HbA_{1c}$ compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in $HbA_{1c}$ compared to metformin.<br><br>Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin.<br><br>Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides.<br><br>There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes.<br><br>There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of |

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| | | | | life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization Diabetes Treatment Satisfaction Questionnaire improved significantly in patients receiving repaglinide compared to patients receiving placebo. |
| Bayraktar et al.[81] (1996)<br><br>Metformin 500 mg TID and sulfonylurea<br><br>vs<br><br>acarbose 50 to 100 mg TID and sulfonylurea | RCT, XO<br><br>Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, $HbA_{1c}$ >8.5%, FPG >7.7 mmol/L, or a PPG>10 mmol/L on maximum doses of gliclazide† (240 mg daily) | N=18<br><br>20 weeks | Primary:<br>Changes in FPG, PPG, $HbA_{1c}$, TG, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline<br><br>Secondary:<br>Not reported | Primary:<br>Mean FPG, PPG, and $HbA_{1c}$ decreased at the end of each combination treatment period as compared with baseline levels (P<0.05).<br><br>PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05).<br><br>There was a significant decrease between pre- and posttreatment two-hour PPG levels in each group (-5.3±0.4 for acarbose vs -2.9±0.3 for metformin, P<0.05).<br><br>There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant.<br><br>Secondary:<br>Not reported |
| Abbasi et al.[82] (2004)<br><br>Metformin 500 to 1,000 mg BID added to existing sulfonylurea monotherapy<br><br>vs<br><br>metformin 500 to 1,000 mg BID added to existing dietary therapy | RCT<br><br>Patients with type 2 diabetes with relatively poor glycemic control with FPG >9.5 mmol/L on dietary therapy alone or sulfonylurea monotherapy, BMI <40 $kg/m^2$, and no apparent cardiovascular disease | N=31<br><br>12 weeks | Primary:<br>Changes in fasting glucose, $HbA_{1c}$, lipid concentrations<br><br>Secondary:<br>Not reported | Primary:<br>FPG decreased to a similar degree with diet therapy (metformin) (12.45±0.48 vs 9.46±0.47 mmol/L; P<0.001) and combined sulfonylurea plus metformin (14.09±0.51 vs 10.57±0.85 mmol/L; P=0.001). The changes in the diet therapy (metformin) group compared to the combined sulfonylurea plus metformin group was not significant (P=0.58).<br><br>Changes in fasting $HbA_{1c}$ from baseline were significant for diet therapy (metformin) (P<0.001) and combined sulfonylurea plus metformin (P<0.002). The changes were not significant when compared to each other (P=0.30).<br><br>Fasting TC, TG, HDL-C, and LDL-C did not change significantly in either treatment group (P=0.64, P=0.34, P=0.48, and P=0.85, respectively) for diet therapy (metformin) compared to combined sulfonylurea plus metformin. |

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| | | | | Fasting remnant lipoprotein cholesterol concentrations were significantly lower in the diet therapy (metformin) group as compared to baseline (0.43±0.09 vs 0.34±0.07 mmol/L; P=0.02). The changes were not significant for diet therapy (metformin) compared to combined sulfonylurea plus metformin (P=0.06).<br><br>Concentrations of FFA and remnant lipoprotein cholesterol concentrations were lower to a similar degree in both groups, whereas day long plasma insulin concentrations were unchanged. Changes in LDL particle diameter and percent of small dense LDL particles between the groups were not significant at end point (P=0.28 and P=0.73, respectively).<br><br>Secondary:<br>Not reported |
| DeFronzo et al.[83] (1995)<br><br>Protocol 1:<br>Metformin 850 to 2,550 mg daily<br><br>vs<br><br>placebo<br><br>Protocol 2:<br>Metformin plus glyburide<br><br>vs<br><br>metformin 500 to 2,500 mg daily<br><br>vs<br><br>glyburide 5 to 10 | 2 DB, PG, RCT<br><br>Moderately obese patients with type 2 diabetes inadequately controlled by diet (Protocol 1) or diet plus glyburide (Protocol 2) | Protocol 1<br>N=289<br>29 weeks<br><br>Protocol 2<br>N=632<br>29 weeks | Primary:<br>Changes in plasma glucose, $HbA_{1c}$, plasma insulin, lipids, plasma lactate<br><br>Secondary:<br>Not reported | Primary:<br>Protocol 1:<br>As compared to the placebo group, the metformin group had lower mean FPG concentrations (189±5 vs 244±6 mg/dL; P<0.001). $HbA_{1c}$ levels were also lower in the metformin group (7.1±0.1 vs 8.6±0.2%; P<0.001).<br><br>The changes from baseline for TC and LDL-C for metformin were significant compared to placebo (P=0.001 and P=0.019, respectively).<br><br>Fasting plasma lactate levels were similar at all times during the active-treatment in both groups.<br><br>Protocol 2:<br>Patients in the metformin plus glyburide combination group, compared to the glyburide alone group, had lower mean FPG concentrations (187±4 vs 261±4 mg/dL; P<0.001), and $HbA_{1c}$ values (7.1±0.1 vs 8.7±0.1%; P<0.001). The effect of metformin alone was similar to that of glyburide alone.<br><br>The changes from baseline were significant compared to glyburide for the following: TC, metformin (P=0.011) and metformin plus glyburide (P=0.001); LDL-C, metformin (P=0.009) and metformin plus glyburide (P=0.001); and TG, each glyburide and metformin plus glyburide |

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| mg BID | | | | (P=0.001)<br><br>Fasting plasma lactate did not change in any of the groups in the course of treatment.<br><br>Secondary:<br>Not reported |
| Goldstein et al.[84] (2003)<br><br>Metformin 500 to 2,000 mg daily<br><br>vs<br><br>glipizide 15 mg BID<br><br>vs<br><br>glipizide/ metformin 5/500 mg daily (dose titrated up to 4 tablets per day) | DB, MC, PG, RCT<br><br>Patients with type 2 diabetes and inadequate glucose control ($HbA_{1c}$ 7.5 to 12.0%) despite monotherapy with at least half the maximum labeled daily dose of a sulfonylurea, FPG <300 mg/dL, and BMI ≥25 to ≤40 $kg/m^2$ | N=247<br><br>18 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Changes in FPG, three-hour PPG, area under the concentration-time curve (AUC), three-hour postprandial insulin incremental AUC during three hours after a standard test meal, fasting insulin level, serum lipid profiles, body weight | Primary:<br>The decreases in $HbA_{1c}$ were significantly greater in the glipizide/metformin group compared to either of the monotherapy groups (P<0.001). A total of 36.6% of patients receiving glipizide/metformin, 8.9% of patients receiving glipizide, and 9.9% of patients receiving metformin had an $HbA_{1c}$ <7.0% at the final visit.<br><br>Secondary:<br>Combination therapy reduced the FPG from baseline significantly more compared to glipizide and metformin monotherapies (P<0.001).<br><br>Combination therapy controlled PPG more than metformin monotherapy or glipizide monotherapy, as measured using a three-hour incremental AUC (P=0.002, and P<0.001, respectively).<br><br>The postprandial insulin three-hour incremental AUC increased from baseline with combination therapy, and decreased with glipizide monotherapy; the differences between these groups were not significant. There was a decrease in the postprandial insulin AUC in the metformin monotherapy group, which was significant (P<0.001 vs combination group).<br><br>Fasting insulin decreased in the combination therapy group and in the metformin monotherapy group. Fasting insulin increased in the glipizide monotherapy group. The changes in the combination therapy group did not differ significantly from either monotherapy group.<br><br>There were decreases in body weight in all groups, -0.3 kg with the combination therapy group, -0.4 kg with the glipizide monotherapy group, and -2.7 kg in the metformin monotherapy group. The changes in the |

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| | | | | metformin monotherapy group were significant compared to the combination therapy group (P<0.001).<br><br>There were no significant changes in the fasting lipid profile in the combination group or metformin monotherapy group. There were significant increases from baseline in TC and TG in the glipizide monotherapy group. |
| Garber et al.[85] (2002)<br><br>Metformin 500 mg daily<br><br>vs<br><br>glyburide 2.5 mg daily<br><br>vs<br><br>glyburide/ metformin 1.25/250 mg daily<br><br>vs<br><br>glyburide/ metformin 2.5/500 mg daily<br><br>vs<br><br>placebo<br><br>Doses were titrated to a maximum of 4 tablets per day. | DB, MC, PC, PG, RCT<br><br>Patients with type 2 diabetes with inadequate glycemic control with diet and exercise, $HbA_{1c}$ >7.0%, normal renal and liver function, and a BMI ≤38 kg/m$^2$ | N=806<br><br>20 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Changes in FPG, two-hour PPG, fasting and two-hour insulin levels, serum lipid concentrations, body weight | Primary:<br>Patients in both glyburide/metformin groups had significantly greater mean reduction from baseline $HbA_{1c}$ (level of 8.2%) compared to the placebo group (P<0.001). The reductions in $HbA_{1c}$ from baseline for each glyburide/metformin group were significantly greater than the placebo or metformin groups (P<0.001). The reduction in $HbA_{1c}$ in the glyburide/metformin 1.25/250 mg group was significantly greater compared to the glyburide group (P<0.016), and for the glyburide/metformin 2.5/500 mg group compared to the glyburide group (P<0.004).<br><br>Sixty-six percent of the patients in the glyburide/metformin 1.25/250 mg group (P=0.006 vs metformin) and 72% of the patients in the glyburide/metformin 2.5/500 mg group (P<0.001 vs metformin, P=0.037 vs glyburide) had achieved an $HbA_{1c}$ <7.0% compared to 60% of the patients in the glyburide group, 50%of patients in the metformin group, and 20% of patients in the placebo group.<br><br>Secondary:<br>Mean decreases in FPG concentrations were significantly greater for both combination groups compared to the placebo (P<0.001) and metformin groups (P<0.001). Mean decreases in FPG were numerically greater in both combination groups compared to the glyburide group, but the differences were not significant.<br><br>Glyburide/metformin 1.25/250 mg group, glyburide/metformin 2.5/500 mg group, and the glyburide group had modest changes in body weight of 1.4, 1.9, and 1.7 kg, respectively, compared to 0.7 and 0.6 kg mean decrease in patients receiving placebo and metformin, respectively. The mean changes in body weight for the glyburide/metformin groups and the |

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| | | | | glyburide group were significantly different from placebo.<br><br>There were no significant changes seen in TC, LDL-C, or HDL-C, and TGs with any treatment. |
| Marre et al.[86] (2002)<br><br>Metformin 500 mg daily<br><br>vs<br><br>glyburide 5 mg daily<br><br>vs<br><br>glyburide/ metformin 2.5/500 mg daily<br><br>vs<br><br>glyburide/ metformin 5/500 mg daily<br><br>Doses were titrated to a maximum of 4 tablets per day. | DB, MC, PG, RCT<br><br>Patients >18 years of age with type 2 diabetes with a FPG ≥126 mg/dL despite treatment with monotherapy metformin ≥850 mg BID or ≥500 mg TID, diet, and exercise for 2 months prior to enrollment, and BMI <40 kg/m$^2$ | N=411<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Changes in FPG, fructosamine levels | Primary:<br>Mean $HbA_{1c}$ levels improved in all groups. There were significantly greater reductions in the patients receiving combination therapy as compared to either monotherapy (P<0.05). There were no significant differences in the amount of the reductions in the $HbA_{1c}$ between the two combination therapies or the two monotherapies.<br><br>Seventy-five percent of the glyburide/metformin 2.5/500 mg group and 63.8% of the glyburide/metformin 5/500 mg group achieved an $HbA_{1c}$ <7.0% as compared to the metformin (37.6%) or glyburide (41.9%) groups (P=0.001 for both).<br><br>Secondary:<br>FPG decreased in all groups. There were significant improvements in both the combination groups compared to either monotherapy (P<0.05). There were no significant differences in effects on FPG between either of the combination therapies or the monotherapies.<br><br>Mean decreases in fructosamine in both combination groups were significantly greater (P<0.05) compared to the changes seen in the monotherapy groups. |
| Johnson et al.[87] (2005)<br><br>Metformin and sulfonylurea<br><br>vs | RETRO<br><br>Patients ≥30 years of age who were new users of oral antidiabetic drugs (sulfonylurea | N=4,124<br><br>N=2,138 sulfonylurea monotherapy<br><br>N=923 | Primary:<br>Composite end point of fatal or nonfatal cardiovascular related events | Primary:<br>A total of 381 patients died from cardiovascular causes and 715 were hospitalized at least once for cardiovascular reasons. Patients in the metformin monotherapy group had the lowest nonfatal hospitalization rate for cardiovascular causes (53.7 hospitalizations per 1,000 person years) compared to sulfonylurea monotherapy patients (75.3 per 1,000 person years; P<0.05) and compared to combination therapy patients (90.2 per |

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| metformin monotherapy<br><br>vs<br><br>sulfonylurea monotherapy | monotherapy, metformin monotherapy, or combination therapy of sulfonylureas and metformin) | metformin monotherapy<br><br>N=1,081 combination therapy<br><br>Duration not reported | Secondary:<br>Not reported | 1,000 person years; P<0.05). Nonfatal cardiovascular related hospitalization rates were similar for sulfonylurea monotherapy patients and combination therapy patients (P=0.08).<br><br>Metformin monotherapy was associated with a lower risk of the composite end point (adjusted HR, 0.81; 95% CI, 0.68 to 0.97) as compared to sulfonylurea monotherapy.<br><br>Cardiovascular hospitalizations were similar for sulfonylurea monotherapy and combination therapy (P=0.32).<br><br>Secondary:<br>Not reported |
| Duckworth et al.[88] (2003)<br><br>Glyburide/ metformin | RETRO<br><br>Patients 18 to 80 years of age with type 2 diabetes were eligible if they had received a combination product with glyburide and metformin for ≥90 days and had been treated with glipizide or glyburide plus metformin for ≥6 months prior to switching to the combination product of glyburide/ metformin | N=72<br><br>196 days (mean follow-up) | Primary:<br>Changes in $HbA_{1c}$, lipid parameters, weight<br><br>Secondary:<br>Not reported | Primary:<br>The mean baseline $HbA_{1c}$ in the total population was 8.3±1.7%. The mean reduction in $HbA_{1c}$ was 0.6% (P=0.002) with a mean follow-up of 196 days after the initiation of glyburide/metformin. The mean daily doses of glyburide and metformin at baseline and at final follow-up were 17.2 and 1,607 mg and 14.7 and 1,750 mg, respectively.<br><br>The greatest decrease in $HbA_{1c}$ was observed in patients with a baseline $HbA_{1c}$ ≥8.0% (n=37). This group had a mean reduction of $HbA_{1c}$ of 1.3% (P=0.0002) with similar doses of glyburide (14.7 vs 16.9 mg; P=0.077) and metformin (1,743 vs 1,624 mg; P=0.11) in both treatment periods.<br><br>There were no significant changes in TC, HDL-C, LDL-C, or TG from baseline.<br><br>There were no significant changes in body weight from a baseline level of 104.3 kg to the last follow-up weight of 104.0 kg (P=0.0645).<br><br>There were no significant differences in patient adherence to the regimen (92.4% before vs 90.9% after).<br><br>Secondary:<br>Not reported |
| Blonde et al.[89] | RETRO | N=1,421 | Primary: | Primary: |

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| (2003)<br><br>Glyburide coadministered with metformin<br><br>vs<br><br>glyburide/ metformin | Patients with type 2 diabetes new to the combination product glyburide/ metformin or glyburide coadministered with metformin between August 2000 and July 2001 and had $HbA_{1c}$ levels at baseline within 79 to 194 days of initiating combination therapy | ~ 6 month (follow-up period) | Change in $HbA_{1c}$<br><br>Secondary:<br>Not reported | The mean $HbA_{1c}$ for the two groups at baseline were similar, 9.1% for the combination product and 9.2% for the individual agents coadministered. During the follow-up period, patients taking the combination product had a lower mean daily dose of glyburide and metformin than patients receiving the individual agents coadministered regardless of baseline $HbA_{1c}$.<br><br>Fifty-six percent of patients in the combination group achieved an $HbA_{1c}$ <7.0% compared to 31.2% of patients receiving the individual agents coadministered. The mean $HbA_{1c}$ decrease from baseline in the combination group was -2.02% and -1.49% when the individual agents were coadministered. The regression results indicated that patients taking the combination product had a significantly greater (P<0.0001) reduction in $HbA_{1c}$ than patients receiving the individual agents coadministered.<br><br>Patients receiving the combination product with baseline $HbA_{1c}$ ≥8.0% experienced a significantly (P<0.0001) greater decrease in $HbA_{1c}$ of 2.93% compared to 1.92% for the individual agents coadministered.<br><br>For patients with baseline $HbA_{1c}$ <8.0%, the difference between the $HbA_{1c}$ responses remained significant. The reductions in $HbA_{1c}$ were smaller for both the combination product and the individual agents coadministered (-0.54 and -0.23%; P=0.0017).<br><br>Patients were more adherent with the combination product than the individual agents coadministered (84% days with drug supply vs 76% days with drug supply, respectively; P<0.0001). The mean decreases in $HbA_{1c}$ were similar for those patients ≥80% adherent and <80% adherent for the combination product (2.12 vs 2.19%; P value not significant) and the individual agents coadministered (1.47 vs 1.24%; P value not significant).<br><br>Secondary:<br>Not reported |
| Lewin et al.[90]<br>(2007) | DB, MC, RCT<br><br>Type 2 diabetic | N=607<br><br>30 weeks | Primary:<br>Change baseline $HbA_{1c}$ | Primary:<br>There were significant reductions in $HbA_{1c}$ from baseline to week 30 in all combined metformin and sulfonylurea groups compared to the |

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| Metformin XR (Glumetza®) 1,500 mg QD, 2,000 mg QD, or 1,000 mg BID and glyburide 15 mg QD<br><br>vs<br><br>glyburide 15 mg QD | patients 18 to 79 years of age, drug naïve or previously treated with oral antidiabetic medications (monotherapy with any oral antidiabetic medications up to half the maximum therapeutic dose), $HbA_{1c}$ 7.5 to 12.0% in drug-naïve patients or 6.5 to 12.0% in prior drug treatment patients, FPG 200 to 400 mg/dL (drug naïve patients) or 120 to 250 mg/dL (prior drug treatment patients) and C-peptide levels >0.8 ng/mL | | Secondary:<br>Changes in $HbA_{1c}$ and FPG at week eight, fructosamine, TC, HDL-C, LDL-C, TG, weight, BMI, discontinuation rates, adverse events | sulfonylurea monotherapy group (-0.74 vs 0.08%, respectively; P<0.001).<br><br>Secondary:<br>There were significant reductions from baseline in mean FPG and in mean $HbA_{1c}$ at week eight in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (P<0.001).<br><br>There were significant differences between the combined metformin and sulfonylurea groups and the monotherapy group for mean changes in fructosamine, TC, HDL-C, and LDL-C (P<0.001 for all).<br><br>There were significant increases from baseline in mean weight and BMI in the monotherapy sulfonylurea group (P<0.001). In comparison, there was no significant change in weight and a smaller increase in mean BMI in the combined metformin and sulfonylurea groups (P=0.028).<br><br>There was a significant difference in the rates of hypoglycemia between groups, which were 11.6% in the combined metformin and sulfonylurea groups and 4.2% in the monotherapy sulfonylurea group (P=0.007). However, no significant difference between these two groups was observed for gastrointestinal events.<br><br>Forty patients (9.3%) in the combined metformin and sulfonylurea groups and three patients (2.1%) in the monotherapy sulfonylurea group discontinued treatment due to an adverse event, mainly hypoglycemia (P=0.001). |
| Chien et al.[91] (2007)<br><br>Metformin 500 mg BID<br><br>vs<br><br>glyburide 5 mg BID | DB, MC, PG, RCT<br><br>Patients 30 to 75 years of age with type 2 diabetes, BMI 18.5 to 35.0 $kg/m^2$, FPG 140 to 250 mg/dL, and $HbA_{1c}$ 7.0 to 12.0% at the screening visit and FPG ≥140 | N=100<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, adverse events | Primary:<br>After 16 weeks, the $HbA_{1c}$ increased in patients receiving glyburide (0.52%; P=0.0018) and there was no change in patients receiving metformin (0.09%; P value not significant).<br><br>After 16 weeks, treatment with glyburide/metformin 2.5/500 mg resulted in a greater reduction in $HbA_{1c}$ compared to glyburide or metformin (-1.77%; P<0.001 and -1.34%; P=0.002). Treatment with glyburide/metformin 5/500 mg resulted in a greater reduction in $HbA_{1c}$ compared to glyburide or metformin alone (-1.73%; P<0.001 and -1.30%; P=0.005). |

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| vs<br><br>glyburide/ metformin 2.5/500mg BID<br><br>vs<br><br>glyburide/ metformin 5/500 mg BID<br><br>The doses were titrated every 2 weeks to a maximum of 4 tablets per day if the exceeded 140 mg/dL. | mg/dL at the second visit, maintained stable sulfonylurea regimen, with or without metformin use | | | After 16 weeks, 19 and 24% of patients in the glyburide/metformin groups (2.5/500 mg and 5/500 mg, respectively) had an $HbA_{1c}$ <7.0% compared to 12.0% in the metformin monotherapy group and 6% in the glyburide monotherapy group.<br><br>Secondary:<br>Mean changes in FPG from baseline were -43 mg/dL in the glyburide group, -41 mg/dL in the metformin group, -98 mg/dL in the glyburide/metformin 2.5/500mg group, and -101 mg/dL in the glyburide/metformin 5/500 mg group. The two glyburide/metformin groups had significant reductions from baseline compared to the monotherapy groups (P<0.0125 compared to glyburide and metformin).<br><br>Treatment with glyburide/metformin 2.5/500 mg resulted in a 55 mg/dL reduction in FPG compared to glyburide (P=0.001) and a 57 mg/dL reduction in FPG compared to metformin (P=0.001). Treatment with glyburide/metformin 5/500 mg resulted in a in a 58 mg/dL reduction in FPG compared to glyburide (P<0.001) and a 60 mg/dL reduction in FPG compared to metformin (P=0.001).<br><br>Ninety-eight episodes of adverse events were reported from the screening visit to the end of the study. Four (14.3%) patients reported adverse events associated with hypoglycemia in the glyburide/metformin 2.5/500 mg group, and two (8.3%) patients reported adverse events associated with gastrointestinal disease among all patients who took metformin during the entire course of the study. The highest incidence of gastrointestinal adverse effects was 32.0% in metformin group, and the lowest was 7.7% in the glyburide/metformin 2.5/500 mg group (P=0.021). |
| Einhorn et al.[92] (2000)<br><br>Metformin (existing therapy)<br><br>vs | DB, PC, RCT<br><br>Patients with poorly controlled type 2 diabetes ($HbA_{1c}$ ≥8.0%) with metformin monotherapy | N=328<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$, FPG, insulin, lipoproteins, and C-peptide<br><br>Secondary:<br>Not reported | Primary:<br>Reductions in $HbA_{1c}$ with pioglitazone add-on therapy were significantly lower compared to placebo (-0.83% difference between treatment groups; P≤0.05).<br><br>Reductions in FPG with pioglitazone add-on therapy were significantly lower compared to placebo (-37.7 mg/dL difference between treatment groups; P≤0.05). |

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| metformin (existing therapy) and pioglitazone 30 to 45 mg | | | | Pioglitazone reduced fasting C-peptide levels (-0.1 ng/mL) while placebo increased levels (0.1 ng/mL; P≤0.05).<br><br>Pioglitazone reduced fasting C-insulin levels (-2.1 ng/mL) while placebo increased levels (0.4 ng/mL; P<0.05).<br><br>Pioglitazone add-on therapy significantly reduced TG (-9.7 vs 8.5 mg/dL; P≤0.05) and increased HDL-C (10.2 vs 1.5 mg/dL; P≤0.05) compared to placebo.<br><br>Both treatment groups increased LDL-C (7.7 vs 11.9 mg/dL; P value not significant).<br><br>No significant difference between treatment groups in number of adverse events was observed. Higher rate of edema was reported with pioglitazone (5.9 vs 2.5%).<br><br>Weight loss was observed with placebo (-1.36 kg) while patients receiving pioglitazone had weight gain (0.95 kg; P value not reported).<br><br>Secondary:<br>Not reported |
| Kaku et al.[93] (2009)<br><br>Metformin 500 to 750 mg daily<br><br>vs<br><br>pioglitazone 15 to 30 mg QD and metformin 500 to 750 mg daily | DB, PC, PG, RCT<br><br>Patients 20 to 65 years of age with type 2 diabetes, $HbA_{1c}$ 6.5 to 10.0%, who were drug naïve or on metformin monotherapy | N=169<br><br>28 weeks | Primary:<br>$HbA_{1c}$, FPG, fasting insulin, insulin resistance, lipid parameters<br><br>Secondary:<br>Not reported | Primary:<br>At week 28, mean change in $HbA_{1c}$ from baseline was -0.67% with pioglitazone compared to 0.25% with placebo (P<0.0001).<br><br>More patients receiving pioglitazone achieved an $HbA_{1c}$ <6.5% compared to placebo (38.6 vs 8.1%, respectively; P<0.0001).<br><br>At week 28, mean change in FPG from baseline was -20.5 mg/dL with pioglitazone compared to 1.9 mg/dL with placebo (P<0.0001).<br><br>Mean fasting insulin concentrations were reduced to a greater extent with pioglitazone (-2.15 mU/mL) compared to placebo (-0.38 mU/mL; P=0.021). |

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| | | | | Insulin resistance was reduced more by pioglitazone compared to placebo (-1.34 vs -0.15; P=0.0025).<br><br>The main differences in lipids between pioglitazone compared to placebo were significant increases in TC (P=0.0057) and HDL-C (P<0.0001). Adiponectin levels were significantly increased by pioglitazone compared to placebo (P=0.0001).<br><br>Secondary:<br>Not reported |
| Perez et al.[94] (2009)<br><br>Pioglitazone/ metformin 15/850 mg BID<br><br>vs<br><br>pioglitazone 15 mg BID<br><br>vs<br><br>metformin 850 mg BID | DB, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes, $HbA_{1c}$ 7.5 to 10.0%, BMI ≤45 kg/m$^2$, who were drug naïve | N=600<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>$HbA_{1c}$ responder rate, changes in baseline FPG, fasting insulin, insulin resistance | Primary:<br>At week 24, mean change in $HbA_{1c}$ from baseline was -1.83% with pioglitazone/metformin compared to -0.96% pioglitazone and -0.99% with metformin (P<0.0001 for combination therapy vs either monotherapy).<br><br>Secondary:<br>In the pioglitazone/metformin group, 63.8% achieved $HbA_{1c}$ <7.0% compared to 46.9% with pioglitazone and 38.9% with metformin (P value not reported).<br><br>Pioglitazone/metformin led to the greatest reduction in FPG from baseline to final visit (-39.9 mg/dL) compared to -22.2 mg/dL with pioglitazone and -24.8 mg/dL with metformin (P<0.01 for combination therapy vs either monotherapy).<br><br>Pioglitazone/metformin led to the greatest reduction in fasting insulin from baseline to final visit (-3.91 µIU/mL), followed by pioglitazone (-3.18 µIU/mL). Both reductions were significantly greater compared to metformin (-0.98 µIU/mL; P<0.05).<br><br>At week 24, the greatest decrease in insulin resistance was seen with pioglitazone/metformin and pioglitazone compared to metformin; however, the difference was significant only with pioglitazone/metformin (P<0.01). |
| Seufert et al.[95] (2008) | 2 MC, RCT<br><br>Patients 35 to 75 | N=1,269<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline, | Primary:<br>*Study 1*<br>The mean change in $HbA_{1c}$ from baseline to week 104 was |

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| Study 1<br>Metformin (existing therapy) and pioglitazone 15 to 45 mg QD<br><br>vs<br><br>metformin (existing therapy) and gliclazide† 80 to 320 mg daily<br><br>Study 2<br>Metformin 850 to 2,550 mg daily and sulfonylurea<br><br>vs<br><br>pioglitazone 15 to 45 mg QD and sulfonylurea therapy (existing therapy) | years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy ($HbA_{1c}$ 7.5 to 11.0%), and fasting C-peptide >1.5 ng/mL) | | FPG, glucose excursions using Three hour oral glucose tolerance test, insulin sensitivity<br><br>Secondary:<br>Not reported | -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20).<br><br>The mean change in FPG from baseline to week 104 was -1.8 mmol/L with pioglitazone and metformin compared to -1.1 mmol/L with gliclazide and metformin (P<0.001).<br><br>Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the two-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin.<br><br>Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001).<br><br>*Study 2*<br>The mean change in $HbA_{1c}$ from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173).<br><br>The mean change in FPG from baseline to week 104 was -2.0 mmol/l with pioglitazone and sulfonylurea compared to -1.9 mmol/l with metformin and sulfonylurea (P=0.506).<br><br>The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment.<br><br>Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments).<br><br>Secondary:<br>Not reported |
| Matthews et al.[96] (2005) | DB, RCT | N=630 | Primary:<br>Effect on $HbA_{1c}$ | Primary:<br>Similar reductions in $HbA_{1c}$ were observed in pioglitazone- (-0.99%) and |

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| Metformin (existing therapy) and pioglitazone 15 to 45 mg QD<br><br>vs<br><br>metformin (existing therapy) and gliclazide† 80 to 320 mg QD | Patients with type 2 diabetes that was poorly controlled ($HbA_{1c}$ 7.5 to 11.0%) with metformin monotherapy | 12 months | Secondary:<br>Effect on FPG, insulin, lipoproteins, and C-peptide | gliclazide-treated groups (-1.01%; P=0.837).<br><br>Secondary:<br>Similar reductions in FPG were observed in pioglitazone- (-2.1 mmol/L) and gliclazide- (-1.6 mmol/L) treated groups (P=0.506).<br><br>Gliclazide significantly reduced LDL-C compared to pioglitazone (-4.2 mg/dL vs +10.4 mg/dL; P=0.001).<br><br>Pioglitazone significantly reduced TG (-53.1 vs -19.5 mg/dL; P<0.001) and increased HDL-C (6.9 mg/dL vs no change; P<0.001) compared to gliclazide. |
| Charbonnel et al.[97] (2005)<br><br>Metformin (existing therapy) and pioglitazone 15 to 45 mg QD<br><br>vs<br><br>metformin (existing therapy) and gliclazide† 80 to 320 mg QD | DB, RCT<br><br>Patients with type 2 diabetes that was poorly controlled ($HbA_{1c}$ 7.5 to 11.0%) with metformin monotherapy | N=630<br><br>24 months | Primary:<br>Effect on $HbA_{1c}$<br><br>Secondary:<br>Effect on FPG, insulin, lipoproteins, and C-peptide | Primary:<br>Similar reductions in $HbA_{1c}$ were observed with pioglitazone add-on therapy (-0.89%) and with gliclazide add-on therapy (-0.77%; P=0.200) after two years.<br><br>Secondary:<br>Significant reductions in FPG were observed with pioglitazone add-on therapy (-1.8 mmol/L) compared to gliclazide add-on therapy (-1.1 mmol/L; P<0.001) after two years.<br><br>Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (-6 vs +2 mg/dL; P<0.001).<br><br>Pioglitazone add-on therapy significantly reduced TG (-23 vs -7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy.<br><br>No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported.<br><br>Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg). |
| Hanefeld et al.[98] (2004) | DB, MC, PG, RCT<br><br>Patients with type 2 | N=639<br><br>12 months | Primary:<br>Change in $HbA_{1c}$ | Primary:<br>$HbA_{1c}$ was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments). |

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| Metformin 850 to 2,250 mg daily and sulfonylurea (existing therapy)<br><br>vs<br><br>pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy) | diabetes inadequately controlled on sulfonylurea monotherapy | | Secondary:<br>FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio) | Secondary:<br>FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant.<br><br>Pioglitazone addition to sulfonylurea significantly reduced TG (-16 vs -9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition.<br><br>LDL-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001).<br><br>Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017).<br><br>Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group. |
| Comaschi et al.[99] (2008)<br><br>Metformin/ glibenclamide* 400/2.5 mg<br>1 to 3 tablets daily<br><br>vs<br><br>pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea) | MC, OL, PG, RCT<br><br>Patients ≥35 years of age with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, $HbA_{1c}$ 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L | N=250<br><br>6 months | Primary:<br>Change in $HbA_{1c}$ from baseline to six months<br><br>Secondary:<br>Change in lipid profiles<br>after six months of treatment | Primary:<br>Pioglitazone-based combination therapy and fixed-dose metformin/glibenclamide resulted in similar reductions in $HbA_{1c}$ (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370).<br><br>Secondary:<br>No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479).<br><br>The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001).<br><br>There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677).<br><br>There was no significant change in LDL-C in patients treated with |

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| | | | | pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425)<br><br>There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045). |
| Borges et al.[100] (2011)<br><br>Rosiglitazone/ metformin<br><br>vs<br><br>metformin | DB, MC, RCT<br><br>Drug naïve patients with type 2 diabetes | N=688<br><br>18 months | Primary:<br>Change in baseline $HbA_{1c}$, FPG<br><br>Secondary:<br>Bone mineral density | Primary:<br>Combination therapy was more efficacious in achieving significant reductions in $HbA_{1c}$ (P<0.0001) and FPG (P<0.001) compared to metformin. In addition, more patients achieved $HbA_1c$ and FPG goals with combination therapy compared to metformin.<br><br>Secondary:<br>In a bone substudy, at week 80 combination therapy was associated with significantly lower bone mineral density compared to metformin in the lumbar spine (P<0.0012) and total hip (P=0.0005, respectively). There was no difference between treatments for distal one-third of radius, femoral neck, and total bone mineral densities (P values not reported). |
| Fonseca et al.[101] (2000)<br><br>Metformin 2,500 mg daily<br><br>vs<br><br>metformin 2,500 mg and rosiglitazone 4 mg daily<br><br>vs<br><br>metformin 2,500 mg and rosiglitazone 8 mg daily | DB, PC, RCT<br><br>Patients with poorly controlled type 2 diabetes (mean FPG 140 to 300 mg/dL) with metformin; baseline $HbA_{1c}$ 8.6% in the metformin treatment group, 8.9% in the rosiglitazone/ metformin 4/2,500 mg treatment group and 8.9% in the rosiglitazone/ metformin 8/2,500 mg treatment group; | N=348<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, fructosamine, C-peptide, FFA, lipids, lactate, and estimates of insulin sensitivity (HOMA-S) and β-cell function (HOMA-B)<br><br>Secondary:<br>Not reported | Primary:<br>Addition of rosiglitazone significantly reduced $HbA_{1c}$ in a dose-related fashion from baseline compared to metformin monotherapy. Mean difference from the metformin control group was -1.0% (P<0.001) with rosiglitazone/metformin 4/2,500 mg and -1.2% with rosiglitazone/metformin 8/2,500 mg (P<0.001).<br><br>Mean FPG concentrations were reduced significantly with rosiglitazone/metformin 4/2,500 mg (-33 mg/dL; P<0.0001) and with rosiglitazone/metformin 8/2,500 mg (-48.4 mg/dL; P<0.0001). No significant change in FPG was observed with metformin monotherapy.<br><br>Fructosamine levels were reduced with both rosiglitazone/metformin 4/2,500 mg (-27.9 µmol/L; P value not reported) and rosiglitazone/metformin 8/2,500 mg (-36.8 µmol/L; P value not reported). Fructosamine levels increased with metformin monotherapy (12.3 µmol/L; P value not reported).<br><br>C-peptide values were reduced significantly in all treatment groups |

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| | patients were excluded if they had NYHA class III-IV heart failure, angina, renal or liver disease, symptomatic neuropathy, or prior use of rosiglitazone or insulin | | | compared to baseline (P<0.05).<br><br>FFA levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).<br><br>Significant increases in TC, HDL-C and LDL-C were observed with both rosiglitazone groups when compared to metformin monotherapy group (P<0.05).<br><br>Mean fasting lactate levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).<br><br>Both insulin sensitivity (as measured by HOMA-S) and β-cell function (as measured by HOMA-B) were increased in a dose-dependent fashion with rosiglitazone/metformin compared to metformin monotherapy (P value not reported).<br><br>Secondary:<br>Not reported |
| Weissman et al.[102] (2005)<br><br>Metformin 1,500 mg QD (MET)<br><br>vs<br><br>rosiglitazone 8 mg QD and metformin 1,000 mg QD (RSG + MET) | DB, MC, PG, RCT<br><br>Patients 18 to 75 years of age diagnosed with type 2 diabetes (defined as $HbA_{1c}$ 6.5 to 8.5% for patients receiving combination therapy with metformin and sulfonylurea or $HbA_{1c}$ 7.0 to 10.0% for drug-naïve or patients receiving monotherapy), FPG | N=766<br><br>2-week wash out period followed by 4 to 7 weeks of run-in period and 24 weeks of treatment | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG at week 24, proportion of patients responding to treatment (reduction ≥0.7% for $HbA_{1c}$ and ≥30 mg/dL for FPG at week 24), clinical safety, adverse events, tolerability, clinical laboratory | Primary:<br>After 24 weeks, RSG+MET and MET were both effective in improving $HbA_{1c}$ with mean reductions of -0.93% (95% CI, -1.06 to -0.80) and -0.71% (95% CI, -0.83 to -0.60), respectively, with a mean treatment difference of -0.20% (95% CI, -0.36 to -0.04).<br><br>Secondary:<br>Significant reductions in FPG from baseline were seen in patients receiving RSG+MET (-2.29 mmol/L; 95% CI, -2.59 to -1.99) compared to patients receiving MET (-1.12 mmol/L; 95% CI, -1.43 to -0.82), with a treatment difference of -0.85 mmol/L (95% CI, -1.23 to -0.47).<br><br>The proportion of patients who responded to treatment (reduction in $HbA_{1c}$ ≥0.7%) was greater in the RSG+MET group than the MET group (59.5 and 49.5%, respectively) with the treatment difference of 10% (95% CI, 1.9 to 18.1). |

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| | of 126 to 270 mg/dL and BMI ≥27kg/m$^2$; any subjects previously receiving metformin or metformin and sulfonylurea must have received ≤metformin 1,000 mg/day for at least 3 months prior to study entry and patients must have stopped previous treatment with TZD at least 3 months prior to screening | | tests | The proportion of FPG responders (reduction in FPG ≥30 mg/dL) was also greater in the RSG+MET group than in the MET group (55.0 vs 32.5%, respectively).<br><br>The percentage of patients experiencing a gastrointestinal effect was greater in the MET group compared to the RSG+MET group (38.7 and 27.9%). The odds of experiencing a gastrointestinal side effect were 63% greater for patients receiving MET compared to patients receiving RSG+MET (OR, 1.63; 95% CI, 1.19 to 2.24).<br><br>RSG+MET resulted in a mean weight gain of 1.79 kg (P<0.0001) compared to a mean weight loss of -1.78 kg (P<0.001) with MET.<br><br>There were three deaths during the course of the study with two prior to DB study medication, and one while on RSG+MET; the cause of which was unknown, although it was not considered to be treatment related. |
| Stewart et al.[103] (2006)<br><br>Metformin 3,000 mg/day (MET)<br><br>vs<br><br>metformin 2,000 mg daily and rosiglitazone 8 mg daily<br>(MET + RSG) | DB, MC, PG, RCT<br><br>Type 2 diabetic patients 18 to 70 years of age, who were either antidiabetic-drug-naïve with FPG of 7.0 to 9.0 mmol/L and $HbA_{1c}$ 7.0 to 9.0%, or previously treated with oral antidiabetic monotherapy with FPG 6.0 to 8.0 mmol/L and $HbA_{1c}$ 6.5 to 8.0% | N=526<br><br>32 weeks | Primary:<br>Proportion of patients achieving $HbA_{1c}$ ≤6.5% at week 32, change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving target $HbA_{1c}$ and FPG levels, change in baseline FPG and fasting plasma insulin, change in insulin resistance, pancreatic β-cell function, CRP, lipid parameters | Primary:<br>At week 32, there was a reduction from baseline in mean $HbA_{1c}$ in the MET+RSG group from 7.2 to 6.7% compared to 7.2 to 6.8% in the MET group (P=0.0357).<br><br>Secondary:<br>The proportion of patients achieving $HbA_{1c}$ ≤6.5% at week 32 was similar in the two groups (P=0.095).<br><br>The proportion of patients achieving FPG <7.0 mmol/L at week 32 was 56% in the MET+RSG group compared to 38% in the MET group (OR, 2.33; P<0.0001).<br><br>The reduction in fasting plasma insulin from baseline was greater in the MET+RSG group compared to the MET group (treatment difference, -12.2 pmol/L; P=0.00029).<br><br>Homeostasis model assessment estimated that insulin sensitivity, β-cell function, CRP, and SBP were greater in the MET+RSG group at week 32 |

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| | | | and 24-hour ambulatory BP, safety | compared to the MET group (P<0.05 for all).<br><br>TC, HDL-C, and LDL-C increased, free fatty acids decreased, and TG did not change in the MET+RSG group, whereas in the MET group there were decreases in TC, LDL-C, and TG, and increases in HDL-C and FFA. The difference between the treatments was significant for the above parameters (P<0.05).<br><br>The proportion of patients with reductions in 24-hour mean SBP was greater in the MET+RSG group compared to the MET group (treatment difference, -3.6 mm Hg; P=0.0315).<br><br>The overall incidences of gastrointestinal adverse events were comparable between groups, but there was a lower incidence of diarrhea in the MET+RSG group (8 vs 18%). Hypoglycemia was reported in 17 patients (7%) in the MET+RSG group compared to 10 patients (4%) in the MET group.<br><br>There were greater reductions in mean hemoglobin and hematocrit over 32 weeks in the MET+RSG group compared to the MET group (P<0.0001). |
| Rosak et al.[104] (2005)<br><br>Metformin (existing therapy) and rosiglitazone 4 to 8 mg | OS, PM<br><br>Two studies in which type 2 diabetics on metformin therapy received rosiglitazone add-on therapy; baseline $HbA_{1c}$ was 8.1% in both trials | N=11,014<br><br>6 months | Primary:<br>Change in baseline $HbA_{1c}$, FPG, body weight, and BP<br><br>Secondary:<br>Not reported | Primary:<br>Addition of rosiglitazone significantly reduced $HbA_{1c}$ from baseline (-1.3%; P<0.0001).<br><br>Addition of rosiglitazone significantly reduced FPG from baseline (-47.0 mg/dL; P<0.0001).<br><br>Significant reduction in BP from baseline (-7/-3 mm Hg; P<0.0001) was observed with rosiglitazone add-on therapy.<br><br>Significant reduction in weight (-1.7 kg; P<0.0001) was observed with rosiglitazone add-on therapy.<br><br>Most commonly reported adverse events were weight gain (0.16%) and edema (0.15%).<br><br>Secondary: |

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| | | | | Not reported |
| Bailey et al.[105] (2005)<br><br>Metformin 2,500 to 3,000 mg daily<br><br>vs<br><br>rosiglitazone/ metformin 4/1,000 to 8/2,000 mg daily | DB, MC, PG, RCT<br><br>Patients with type 2 diabetes poorly controlled (FPG ≥126 to 216 mg/dL) with metformin alone or in combination with an insulin secretagogue or acarbose; baseline $HbA_{1c}$ 7.4% for rosiglitazone add-on therapy and 7.5% for metformin; patients were excluded if they had been treated with a TZD or insulin, had unstable cardiovascular or cerebrovascular conditions, or had uncontrolled hypertension | N=568<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and insulin, proportion of patients who achieved $HbA_{1c}$ and FPG targets | Primary:<br>Reductions in $HbA_{1c}$ observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-0.22% difference between treatment groups; P=0.001).<br><br>Secondary:<br>Reductions in FPG observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-18.3 mg/dL difference between treatment groups; P<0.001).<br><br>Significant reduction in fasting insulin was observed with rosiglitazone add-on therapy compared to metformin monotherapy (-12.4 pmol/L difference between treatment groups; P=0.001).<br><br>Greater proportion of patients on rosiglitazone add-on therapy (54%) reached $HbA_{1c}$ targets (<7.0%) compared to those treated with metformin monotherapy (36%; OR, 2.42; P<0.001).<br><br>Greater proportion of patients on rosiglitazone add-on therapy (32%) reached FPG targets (<126 mg/dL) compared to those treated with metformin monotherapy (8%; OR, 5.71; P<0.001).<br><br>Higher rate of withdrawal due to adverse events with metformin monotherapy (8 vs 4%; no P value reported) was noted. Gastrointestinal disorders were the most commonly reported event that caused withdrawal in the metformin monotherapy group. |
| Rosenstock et al.[106] (2006)<br><br>Metformin 500 to 2,000 mg daily<br><br>vs<br><br>rosiglitazone 4 to 8 | DB, MC, RCT<br><br>Type 2 diabetics with $HbA_{1c}$ >7.5 to 11.0%, with FPG ≤270 mg/dL who were previously treated with diet and exercise or had | N=468<br><br>32 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ and FPG targets, change in | Primary:<br>Patients receiving rosiglitazone/metformin showed significant improvements in $HbA_{1c}$ with a reduction of -2.3% compared to baseline vs -1.8% with patients receiving metformin (P<0.0008) and -1.6% with patients receiving rosiglitazone (P<0.0001).<br><br>Secondary:<br>Target $HbA_{1c}$ ≤6.5 and <7.0% were achieved in more patients in the rosiglitazone/metformin group (60 and 77%) than in the metformin (39 |

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| mg daily<br><br>vs<br><br>rosiglitazone/ metformin 4/1,000 to 8/2,000 mg daily | not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening | | baseline FPG, safety | and 57%) or rosiglitazone (35 and 58%) groups, respectively (P values not reported).<br><br>The greatest mean decrease in FPG was seen with rosiglitazone/metformin (-74 mg/dL) and was significant compared to metformin (-50 mg/dL; P<0.0001) and rosiglitazone (-47 mg/dL; P<0.0001).<br><br>Treatment was well tolerated with nausea, vomiting and diarrhea as the most commonly reported adverse events. Edema was comparable between rosiglitazone/metformin (6%) and rosiglitazone (7%) and lower with metformin. |
| TODAY Study Group.[107] (2012) TODAY<br><br>Metformin<br><br>vs<br><br>rosiglitazone 4 mg BID plus metformin<br><br>vs<br><br>metformin plus lifestyle intervention (focusing on weight loss through eating and activity behaviors)<br><br>Patients were treated during a run-in period of 2 | MC, RCT<br><br>Patients 10 to 17 years of age, with type 2 diabetes | N=699<br><br>3.86 years (average follow-up) | Primary:<br>Loss of glycemic control ($HbA_{1c}$ ≥8.0% for six months or sustained metabolic decompensation requiring insulin)<br><br>Secondary:<br>Body weight, metabolic outcomes, safety | Primary:<br>Overall, a total of 319 (45.6%) patients reached the primary outcome, with a median time to treatment failure of 11.5 months (range, <1 to 66). Rates of failure were 51.7 (95% CI, 45.3 to 58.2), 38.6 (95% CI, 32.4 to 44.9), and 46.6% (95% CI, 40.2 to 53.0) of patients on metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention, respectively.<br><br>Rosiglitazone plus metformin was more efficacious to metformin; combination therapy was associated with a 25.3% decrease in the occurrence of the primary outcome compared to metformin (P=0.006). The outcome with metformin plus lifestyle intervention was intermediate, but not significantly different from metformin or rosiglitazone plus metformin (P value not reported). The reasons for treatment failure did not differ significantly across treatments.<br><br>Prespecified analyses according to sex and race or ethnic group showed differences in sustained effectiveness, with metformin least effective in non-Hispanic black patients and rosiglitazone plus metformin most effective in female patients.<br><br>Secondary:<br>BMI over time (up to 60 months) differed significantly according to the study treatment (P<0.001 for the overall comparison), and the results of all three pairwise comparisons between treatment groups were also significant. Patients treated with rosiglitazone plus metformin had the greatest increase in BMI and patients receiving metformin plus lifestyle |

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| to 6 months with metformin 1,000 mg BID to attain an $HbA_{1c}$ <8.0% prior to randomization. | | | | intervention had the least.<br><br>The change in fat mass from baseline differed significantly across the treatment groups (P<0.05) because of a significant difference between rosiglitazone plus metformin and metformin plus lifestyle interventions. There were no significant between-group differences in the change from baseline for any other outcome.<br><br>Serious adverse events were reported in 19.2% of all patients, including 18.1, 14.6, and 24.8% with metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention (P=0.02). Hospitalizations accounted for more than 90% of serious adverse events. Severe hypoglycemia occurred in one, one, and two patients receiving metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention. No effects of rosiglitazone on bone mineral content or rate of fracture were noted. |
| Home et al.[108] (2007)<br>RECORD Interim Analysis<br><br>Metformin plus a sulfonylurea<br><br>vs<br><br>rosiglitazone plus either metformin or a sulfonylurea | MC, OL, RCT<br><br>Patients with type 2 diabetes between the ages of 40 and 75 years, BMI >25.0 kg/m$^2$, $HbA_{1c}$ 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, | N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103 rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea)<br><br>Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be | Primary:<br>Hospitalization or death from cardiovascular causes<br><br>Secondary:<br>Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke | Primary:<br>For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication.<br><br>Secondary:<br>There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI.<br><br>Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006). |

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| | a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension | 6 years) | | |
| Home et al.[109] (2009)<br>RECORD<br><br>Metformin plus a sulfonylurea<br><br>vs<br><br>rosiglitazone plus either metformin or a sulfonylurea | MC, OL, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | N=4,458<br><br>5.5 years (mean follow-up) | Primary:<br>Time to first cardiovascular hospitalization or cardiovascular death<br><br>Secondary:<br>Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke | Primary:<br>The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93).<br><br>Secondary:<br>There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95%, CI 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50).<br><br>Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010).<br><br>There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures. |
| Home et al.[110] | MC, OL, PG, RCT | N=1,122 | Primary: | Primary: |

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| (2007)<br><br>Metformin plus a sulfonylurea<br><br>vs<br><br>rosiglitazone plus either metformin or a sulfonylurea | Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | 18 months | Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell function (HOMA %β), body weight, inflammatory/ thrombotic markers, CRP | At 18 months, $HbA_{1c}$ reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant).<br><br>Secondary:<br>Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089).<br><br>Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for both).<br><br>HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant).<br><br>Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003).<br><br>At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant).<br><br>There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001). |
| Komajda et al.[111] (2008) | MC, OL, RCT | N=668 | Primary:<br>Change from | Primary:<br>For patients receiving rosiglitazone and a sulfonylurea, the reduction in |

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| RECORD<br><br>Metformin plus a sulfonylurea<br><br>vs<br><br>rosiglitazone plus either metformin or a sulfonylurea | Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | 12 months | baseline in 24-hour ambulatory BP at six months and 12 months<br><br>Secondary:<br>Not reported | 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031).<br><br>Reductions in 24-hour DBP were greater at 6 months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001).<br><br>At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016).<br><br>At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mmHg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003).<br><br>At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P value not significant, DBP; P=0.049).<br><br>Secondary:<br>Not reported |
| Hamann et al.[112] (2008)<br><br>Metformin 2,000 mg daily and glibenclamide* 5 mg or gliclazide† 80 mg (SU+MET)<br><br>vs<br><br>rosiglitazone/ metformin fixed dose combination | DB, PG, RCT<br><br>Overweight patients (BMI ≥25 kg/m$^2$) with type 2 diabetes, $HbA_{1c}$ 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks | N=596<br><br>52 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to week 52<br><br>Secondary:<br>Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP | Primary:<br>At week 52, mean change in $HbA_{1c}$ from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25).<br><br>Secondary:<br>Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095).<br><br>The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 $HbA_{1c}$%/year, respectively; P=0.0002).<br><br>Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001). |

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| 4/2,000 mg daily (RSG+MET) | | | | Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001).<br><br>After 52 weeks, 24-hour diastolic and systolic ambulatory BPs were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BPs (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549). |
| **Diabetes Prevention Studies** | | | | |
| Knowler et al.[113] (2002)<br><br>Metformin 850 mg BID<br><br>vs<br><br>placebo with standard lifestyle recommendations<br><br>vs<br><br>intensive lifestyle modifications designed to achieve and maintain both a 7% weight loss and 150 minutes of exercise a week | DB, MC, PC, RCT<br><br>Nondiabetic patients ≥25 years of age at high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥24 kg/m$^2$ or ≥22 kg/m$^2$ for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140 to 199 mg/dL 2 hours after a 75 g oral glucose load | N=3,234<br><br>2.8 years (mean) | Primary:<br>Diabetes, diagnosed on the basis of an annual oral glucose-tolerance test or a semiannual FPG test, according to the 1997 criteria of the American Diabetes Association: a value for plasma glucose of 126 mg/dL or higher in the fasting state or 200 mg/dL or higher two hours after a 75 g oral glucose load<br><br>Secondary:<br>Not reported | Primary:<br>Incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and intensive lifestyle-intervention groups, respectively.<br><br>Incidence of diabetes was 58% lower (95% CI, 48 to 66) in the intensive lifestyle-intervention group and 31% lower (95% CI, 17 to 43) in the metformin group than in the placebo group.<br><br>Incidence of diabetes was 39% lower (95% CI, 24 to 51) in the intensive lifestyle-intervention group than in the metformin group.<br><br>Incidence of diabetes differed significantly among the three groups (P<0.001 for each comparison).<br><br>The estimated cumulative incidence of diabetes at three years was 28.9, 21.7, and 14.4% in the placebo, metformin, and intensive lifestyle groups, respectively. Using these results, to prevent one case of diabetes during a three-year period, 6.9 persons would have to participate in the intensive lifestyle-intervention group and 13.9 persons would have to receive metformin.<br><br>Secondary:<br>Not reported |
| Orchard et al.[114] (2005)<br><br>Metformin 850 mg | DB, MC, PC, RCT<br><br>Nondiabetic patients ≥25 years of age at | N=3,234<br><br>3.2 years (mean) | Primary:<br>Prevalence of the metabolic syndrome at | Primary:<br>Fifty-three percent of the patients fulfilled the criteria for the metabolic syndrome; this proportion was relatively constant by age. |

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| BID<br><br>vs<br><br>placebo with standard lifestyle recommendations<br><br>vs<br><br>intensive lifestyle modifications designed to achieve and maintain a 7% weight loss and 150 minutes of exercise a week | high risk with elevated fasting and post-load plasma glucose concentrations, BMI ≥24 kg/m$^2$ or ≥22 kg/m$^2$ for Asian patients, a plasma glucose concentration 95 to 125 mg/dL, and 140 to 199 mg/dL two hours after a 75 gram oral glucose load | | baseline in the Diabetes Prevention Program and the incidence of new cases after intensive lifestyle intervention and metformin<br><br>Secondary:<br>Not reported | Incidence of the metabolic syndrome was reduced by 41% in the intensive lifestyle group (P<0.001) and by 17% in the metformin group (P=0.03) compared to the placebo group.<br><br>Resolution of metabolic syndrome in participants who had the syndrome at baseline was significant for intensive lifestyle interventions vs placebo (P=0.002). The prevalence at three years varied significantly by treatment group (P<0.001): 18% of the placebo group, 23% of the metformin group, and 38% of the intensive lifestyle group no longer had the syndrome.<br><br>Prevalence of the metabolic syndrome in all participants increased from 55% at baseline to 61% after three years in the placebo group (P=0.003) and from 54% to 55% in the metformin group (P>0.2), but decreased in the intensive lifestyle group from 51 to 43% (P<0.001).<br><br>Three-year cumulative incidences of the metabolic syndrome were 51% for placebo, 45% for metformin, and 34% for intensive lifestyle groups.<br><br>Secondary:<br>Not reported |
| Zinman et al.[115]<br>CANOE<br><br>Rosiglitazone 2 mg/day plus metformin 500 mg BID<br><br>vs<br><br>placebo | DB, RCT<br><br>Patients with impaired glucose tolerance | N=207<br><br>3.9 years (median duration) | Primary:<br>Time to development of diabetes<br><br>Secondary:<br>Insulin sensitivity, β cell function, safety | Primary:<br>Incident diabetes occurred in significantly fewer patients receiving combination therapy compared to placebo (14 vs 39%; P<0.0001). The relative risk reduction was 66% (95% CI, 48 to 80) and the absolute risk reduction was 26% (95% CI, 14 to 37), yielding a number needed to treat of 4 (95% CI, 2.70 to 7.14).<br><br>Seventy patients (80%) receiving combination therapy regressed to normal glucose tolerance compared to 52 patients (53%) receiving placebo (P=0.0002).<br><br>Secondary:<br>Insulin sensitivity decreased by trial end in patients receiving placebo (median, -1.24) and remained unchanged in patients receiving combination therapy (median, -0.39; P=0.0006 vs placebo).<br><br>Change in β cell function did not differ between the two treatments |

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| | | | | (P=0.28).<br><br>Significantly more patients receiving combination therapy experienced diarrhea compared to placebo (P=0.0253). |
| Van de Laar et al.[116]<br>(2006)<br><br>Metformin<br><br>vs<br><br>acarbose,<br>placebo,<br>diet and exercise,<br>or both | MA (5 trials)<br><br>Patients with impaired glucose tolerance or impaired fasting blood glucose | N=2,360<br><br>1 to 6 years | Primary:<br>Occurrence of type 2 diabetes<br><br>Secondary:<br>Cardiovascular morbidity and mortality, glycemic control, lipids, BP, body weight | Primary:<br>In the comparison of acarbose to placebo, the incidence of or conversion to type 2 diabetes was reduced [RR, 0.78; 95% CI, 0.68 to 0.90].<br><br>Neither acarbose nor metformin had significant effects on the incidence of type 2 diabetes when compared to one another. However, when compared to diet and exercise, acarbose had beneficial effects on the incidence of type 2 diabetes (RR, 0.40; 95% CI, 0.17 to 0.96).<br><br>Secondary:<br>There were no significant effects on total mortality or mortality due to cardiovascular causes in trials comparing acarbose to placebo. In one trial (STOP-NIDDM), a decreasing effect on the incidence of cardiovascular disease as a combined end point (MI, angina, revascularization procedures, cardiovascular death, congestive heart failure, cerebrovascular events, and peripheral vascular disease) was reported (RR, 0.47; 95% CI, 0.26 to 0.86).<br><br>Acarbose decreased PPG by 0.61 mmol/L (95% CI, 0.27 to 0.95) compared to placebo. In the EDIT study, acarbose significantly decreased FPG and PPG in comparison to placebo (P=0.0043 and P=0.0075, respectively). In comparison to metformin, acarbose showed a decreasing effect on PPG (1.40 mmol/L; 95% CI, 0.55 to 2.25). Similarly, acarbose vs diet and exercise also showed significant reductions in FPG and PPG (-1.37 [95% CI, -0.50 to -2.24] and -2.79 mmol/L [95% CI, -1.79 to -3.79]).<br><br>There were no significant effects on DBP and SBP in trials comparing acarbose to placebo. However, metformin showed significant decreases in both TC and DBP in comparison to acarbose (0.90 mmol/L [95% CI, 0.19 to 1.61] and 6 mm Hg [95% CI, 2.81 to 9.19], respectively).<br><br>Acarbose decreased body weight by 1.2 kg (95% CI, 0.5 to 1.8) and BMI by 0.3 kg/m$^2$ (95% CI, 0.1 to 0.5) compared to placebo. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Salpeter et al.[117] (2008)<br><br>Metformin (variable doses)<br><br>vs<br><br>placebo or no treatment | MA (31 RCTs)<br><br>Patients at risk for type 2 diabetes mellitus | N=4,570<br><br>Duration varied | Primary:<br>BMI, fasting glucose, fasting insulin, calculated insulin resistance, HDL-C, LDL-C, TG, incidence of new-onset diabetes<br><br>Secondary:<br>Not reported | Primary:<br>Pooled results showed that metformin reduced BMI (-5.3%; 95% CI, -6.7 to -4.0), fasting glucose (-4.5%; 95% CI, -6.0 to -3.0), fasting insulin (-14.4%; 95% CI, -19.9 to -8.9), insulin resistance (-22.6%; 95% CI, -27.3 to -18.0), TG (-5.3%; 95% CI, -10.5 to -0.03), and LDL-C (-5.6%; 95% CI, -8.3 to -3.0%), and increased HDL-C (5.0%; 95% CI, 1.6 to 8.3) compared to placebo or no treatment.<br><br>The incidence of new-onset diabetes was reduced by 40% (OR, 0.6; 95% CI, 0.5 to 0.8), with an absolute risk reduction of 6% (95% CI, 4 to 8) during a mean trial duration of 1.8 years.<br><br>Secondary:<br>Not reported |
| **Gestational Diabetes** | | | | |
| Moore et al.[118] (2010)<br><br>Metformin 500 to 2,000 mg daily (divided doses)<br><br>vs<br><br>glyburide 2.5 to 10 mg BID<br><br>Insulin was started in treatment failures and oral medication was discontinued. | DB, PG, RCT<br><br>Women with gestational diabetes between 11 and 33 weeks gestation at the time of randomization | N=149<br><br>Variable duration | Primary:<br>Glycemic control<br><br>Secondary:<br>Medication failure rate, macrosomia, admission to the neonatal intensive care unit, five-minute Apgar score less <7, birth trauma, preeclampsia, maternal and neonatal hypoglycemia, and route of delivery | Primary:<br>There was no difference between the glyburide or metformin groups in mean fasting (P=0.23) or two-hour PPG concentrations (post-breakfast, P=0.15; post-lunch, P=0.28; post-dinner, P=0.32).<br><br>Secondary:<br>Twenty-six patients (34.7%) in the metformin group and 12 patients (16.2%) in the glyburide group did not meet glycemic goals and required insulin therapy (P=0.01). The failure rate of metformin was 2.1 times higher than the failure rate of glyburide (95% CI, 1.2 to 3.9, OR, 2.7).<br><br>Macrosomia occurred in 5.4% of patients in the glyburide group and 1.3% of patients in the metformin group (P=0.20). The mean birth weight of babies in the metformin group was smaller than the mean birth weight of babies in the glyburide group (P=0.02). Other neonatal outcomes did not differ between the two groups.<br><br>There were four neonatal intensive care unit admissions in the metformin group and one neonatal intensive care unit admission in the glyburide group (P=0.37).<br><br>There were no 5-minute Apgar scores <7 in either group. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | There was one shoulder dystocia in the glyburide group and one third-degree tear in the metformin group (P=0.49).<br><br>The incidence of maternal hypoglycemia and preeclampsia was not different between the two treatment groups (P=0.56 and P>0.50, respectively). One infant in the metformin group experienced hypoglycemia with blood glucose less than 40 mg/dL.<br><br>Excluding elective repeat cesarean deliveries, there were 11 cesarean deliveries in the metformin group compared with two cesarean deliveries in the glyburide group (P=0.02). |

*Synonym for glyburide.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily, XR=extended-release
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PM=post-marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: apo=apolipoprotein, AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, $HbA_{1c}$=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta cell function, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, IU=international units, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PPG=postprandial plasma glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TNF=Tumor necrosis factor, TZD=thiazolidinedione, WMD=weighted mean difference

**Additional Evidence**

Dose Simplification
Schwartz et al. compared the efficacy, tolerability and safety of metformin immediate-release tablets and metformin extended-release tablets. Patients received a dose of 1,500 mg once daily, 1,500 mg twice daily or 2,000 mg once daily of metformin extended-release or 1,500 mg daily of metformin immediate-release given in two divided doses. The investigators demonstrated that once-daily extended-release metformin was as effective as twice-daily immediate-release metformin.[21]

Donnan et al. evaluated the patterns and predictors of adherence in patients with type 2 diabetes receiving treatment with a single antidiabetic agent. Adherence was ≥90% in 31.3% of the patients prescribed sulfonylureas and 33.9% of patients prescribed metformin. Patients with better adherence tended to be younger and had a shorter duration of diabetes. There were linear trends of poorer adherence with each increase in the daily number of tablets taken for both sulfonylurea (P=0.001) and metformin (P=0.074) indices. There were significant trends of decreasing adherence with the number of co-medications for the sulfonylurea group (P=0.0001) and metformin group (P=0.007). This study did not measure the impact of adherence on clinical outcomes.[119]

Stable Therapy
Fujioka et al. evaluated glycemic control in patients with type 2 diabetes mellitus switched from twice-daily immediate-release metformin to a once-daily extended-release formulation. The investigators found comparable efficacy and tolerability among the treatment groups.[20] Bhansali et al. demonstrated similar results when patients were switched from an immediate-release metformin product to an extended-release product. The investigators found that patients receiving immediate-release metformin achieved comparable glycemic control when treatment was switched to a once- or twice-daily metformin extended-release product.[18]

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 11. Relative Cost of the Biguanides**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Metformin | Extended-release tablet, solution, tablet | Fortamet®*, Glucophage®*, Glucophage XR®*, Glumetza®, Riomet® | $$$$$ | $ |

*Generic is available in at least one dosage form or strength.

## X. Conclusions

Metformin in the only biguanide that is currently available and it is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-4] The immediate-release and sustained-release tablets are both available in a generic formulation.

According to current clinical guidelines, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin ($HbA_{1c}$) will most likely require combination or triple therapy in order to achieve glycemic goals, and at this time, there are no uniform recommendations on the best agent to be combined with metformin. Metformin may be considered for the prevention/delay of type 2 diabetes in certain patients. Furthermore, metformin is recommended first-line, and should be initiated at the time of diagnosis, along with lifestyle modifications, unless contraindicated. Metformin is recognized as having high $HbA_{1c}$-lowering potential, a low risk of hypoglycemia, and a weight neutral effect compared to other available antidiabetic medications. Among all current clinical guidelines, no one metformin formulation is recommended or preferred over another.[7-16]

Numerous clinical trials have established the efficacy/safety of metformin as monotherapy, as well as in combination with other antidiabetic agents.[17-119] Studies directly comparing immediate-release and sustained-release formulations of metformin have demonstrated similar efficacy.[18-20]

The most common adverse events with metformin are gastrointestinal in nature and include diarrhea, flatulence, nausea/vomiting, abdominal discomfort and indigestion. There is also a risk of lactic acidosis with metformin. Although it occurs rarely, it can be fatal in approximately 50% of cases. Patients with renal insufficiency, congestive heart failure, hepatic impairment, history of lactic acidosis, decreased tissue perfusion, hemodynamic instability, hypoxic states or serious acute illness are at increased risk of lactic acidosis.[1-4]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin or any other antidiabetic drug.[1-4]

There is insufficient evidence to support that one brand biguanide is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand biguanide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
# AHFS Class 682005
# November 14, 2012

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The DPP-4 inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are human incretin hormones that are released from the small intestine in response to food intake. These hormones have multiple effects on the stomach, liver, pancreas and brain to control glucose concentrations; however, they are inactivated by the DPP-4 enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. The DPP-4 inhibitors slow the inactivation of the incretin hormones and increase their concentration in the bloodstream. This effect enhances glucose-dependent insulin secretion by pancreatic beta cells and suppresses glucagon secretion from pancreatic alpha cells.[1-3]

Linagliptin, saxagliptin, and sitagliptin are also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[4-7] In addition, sitagliptin is available in combination with a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor simvastatin. Simvastatin inhibits HMG-CoA reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate. Conversion to mevalonate is an early and rate limiting step in the biosynthetic pathway for cholesterol. Simvastatin also produces beneficial effects on very low density lipoprotein cholesterol, triglyceride, and high density lipoprotein cholesterol.[8]In general, all of the combination DPP-4 inhibitor products are available for use when treatment with both drug components is appropriate.[4-8]

The DPP-4 inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available; however, metformin and simvastatin are available generically in a separate formulation. This class was last reviewed in May 2010.

**Table 1. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Linagliptin | tablet | Tradjenta® | none |
| Saxagliptin | tablet | Onglyza® | none |
| Sitagliptin | tablet | Januvia® | none |
| **Combination Products** | | | |
| Linagliptin and metformin | tablet | Jentadueto® | none |
| Saxagliptin and metformin | extended-release tablet | Kombiglyze XR® | none |
| Sitagliptin and metformin | extended-release, tablet, tablet | Janumet®, Janumet XR® | none |
| Sitagliptin and simvastatin | tablet | Juvisync® | none |

PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[9] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes<br>• An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Approach[10] (2012)** | first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy.<br><br><u>Initial drug therapy</u><br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br><u>Advancing to dual combination therapy</u><br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.<br>• Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.<br>• It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. |

| Clinical Guideline | Recommendation(s) |
|---|---|

- For all medications, consideration should also be given to overall tolerability.

Advancing to triple combination therapy

- Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
- Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
- In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
- Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

**Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations**

| **Initial Drug Monotherapy** | Metformin |
|---|---|
| Efficacy (↓$HbA_{1c}$) | High |
| Hypoglycemia | Low risk |
| Weight | Neutral/loss |
| Side Effects | Gastrointestinal/lactic acidosis |

If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)

| **Two Drug Combin-ations** | Metformin + sulfonyl-urea | Metformin + thia-zolidinedione (TZD) | Metformin + DPP-4 inhibitor | Metformin + GLP-1 receptor agonist | Metformin + insulin (usually basal) |
|---|---|---|---|---|---|
| Efficacy (↓$HbA_{1c}$) | High | High | Inter-mediate | High | Highest |
| Hypo-glycemia | Moderate risk | Low risk | Low risk | Low risk | High risk |
| Weight | Gain | Gain | Neutral | Loss | Gain |
| Major Side Effects | Hypo-glycemia | Oedema, heart failure, bone fracture | Rare | Gastro-intestinal | Hypo-glycemia |

If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)

| **Three Drug Combin-ations** | Metformin + sulfonyl-urea + | Metformin + TZD + | Metformin + DPP-4 inhibitor + | Metformin + GLP-1 receptor agonist + | Metformin + insulin therapy + |
|---|---|---|---|---|---|
| | TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonyl-urea, TZD, or insulin | Sulfonyl-urea, TZD, or insulin | TZD, DPP-4 inhibitor, or GLP-1 receptor agonist |

If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents

| **More Complex Insulin Strategies** | Insulin (multiple daily doses) |
|---|---|

| Clinical Guideline | Recommendation(s) |
|---|---|
| American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[11] (2012)** | • Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.<br>• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.<br>• It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. |
| American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[12] (2011)** | Antihyperglycemic pharmacotherapy<br>• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[13]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[13] (2009)** | Principles underlying the algorithm<br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action.<br>• Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br>Stratification by current $HbA_{1c}$<br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%<br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss. |

| Clinical Guideline | Recommendation(s) |
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| | • Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + GLP-1 receptor agonist + glinide.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + DPP-4 inhibitor + glinide.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + TZD.<br>  o Metformin + sulfonylurea.<br>  o Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because |

| Clinical Guideline | Recommendation(s) |
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| | the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>  o Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>  o Metformin + TZD.<br>  o Metformin + TZD + sulfonylurea.<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid |

| Clinical Guideline | Recommendation(s) |
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| | onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[14] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>  ○ Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>  ○ Initiate self-monitoring blood glucose levels.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>• First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>• After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>• Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting |

| Clinical Guideline | Recommendation(s) |
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| | blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>• Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>• Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level |

| Clinical Guideline | Recommendation(s) |
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| | is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[15] (2009)** | DPP-4 inhibitors<br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br>TZDs<br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor. |

| Clinical Guideline | Recommendation(s) |
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| | • There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  o A body mass index ≥35 kg/m$^2$ in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI <35 kg/m$^2$, and thera$^p$y with insulin would have significant occupational implications or weight loss would benefit other sig$^n$ificant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  o A person prefers injecting insulin immediately before a meal<br>  o Hypoglycemia is a problem.<br>  o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>  o Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>  o Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>  o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>  o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>• Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone. |

| Clinical Guideline | Recommendation(s) |
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| **Clinical Guideline for Management in Primary and Secondary Care (Update)[16] (2008)** | • Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br><u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>  ○ The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>  ○ A sulfonylurea if metformin is not tolerated.<br>  ○ Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br><u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u><br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  ○ Body mass index >35kg/m$^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  ○ Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  ○ Inadequate blood glucose control ($HbA_{1c}$ ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  ○ Other therapies, such as a thiazolidinedione or insulin |

| Clinical Guideline | Recommendation(s) |
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| | injection therapy, would otherwise be started<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  o Continue with metformin and the sulfonylurea (and acarbose, if used)<br>  o Review the use of the sulfonylurea if hypoglycemia occurs<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>  o Continue with metformin<br>  o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs<br>• Consider combining pioglitazone with insulin therapy for:<br>  o Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>  o Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>  o Those who require assistance from a care taker or healthcare professional to administer their insulin injections<br>  o Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes<br>  o Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ is >9.0%. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>  o Immediate injection before a meal is preferred.<br>  o Hypoglycemia is a problem.<br>  o There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Type 2 Diabetes Mellitus in** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated. |

| Clinical Guideline | Recommendation(s) |
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| **Adults[17] (2012)** | • Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |
| International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes[18] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br>Insulin<br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the dipeptidyl peptidase-4 (DPP-4) inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the DPP-4 Inhibitors[1-8]**

| Generic Name(s) | Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes | Monotherapy or Combination Therapy as Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes | Patients For Whom Treatment With Both Sitagliptin and Simvastatin is Appropriate |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Linagliptin | | ✔ | |
| Saxagliptin | | ✔ | |

| Generic Name(s) | Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes | Monotherapy or Combination Therapy as Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes | Patients For Whom Treatment With Both Sitagliptin and Simvastatin is Appropriate |
|---|---|---|---|
| Sitagliptin | | ✔ | |
| **Combination Products** | | | |
| Linagliptin and metformin | ✔ * | | |
| Saxagliptin and metformin | ✔ † | | |
| Sitagliptin and metformin | ✔ ‡ | | |
| Sitagliptin and simvastatin | | | ✔ § |

*When treatment with both linagliptin and metformin is appropriate.
†When treatment with both saxagliptin and metformin is appropriate.
‡When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.
§Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Simvastatin is indicated as an adjunctive therapy to diet to reduce the risk of total mortality by reducing coronary heart disease deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events; reduce elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides (TG) and increase high density lipoprotein cholesterol in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; reduce elevated TG in patients with hypertriglyceridemia and reduce TG and very low density lipoprotein cholesterol in patients with primary dysbetalipoproteinemia; and reduce TC and LDL-C in patients with primary homozygous familial hypercholesterolemia.

## IV. Pharmacokinetics

The pharmacokinetic parameters of the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the DPP-4 Inhibitors[19]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| **Single Entity Agents** | | | | | |
| Linagliptin | 30 | 70 to 99 | Not reported | Renal (5 to 7), Bile (80) | >100 |
| Saxagliptin | Not reported | Negligible (% not reported) | Liver (% not reported) | Renal (60), Feces (22) | 2.5 |
| Sitagliptin | 87 | 38 | Liver, minimal (% not reported) | Renal (87), Feces (13) | 12.4 |
| **Combination Products** | | | | | |
| Linagliptin and metformin | 30/50 to 60 | 70 to 99/ negligible (% not reported) | Minimal (% not reported)/None | Renal (5 to 7), Bile (80)/ Renal (90) | >100/6.2 |
| Saxagliptin and metformin | Not reported/ 50 to 60 | Negligible (% not reported)/ Negligible (% not reported) | Liver (% not reported)/None | Renal (60), Feces (22)/ Renal (90) | 2.5/6.2 |
| Sitagliptin and metformin | 87/50 to 60 | 38/Negligible (% not reported) | Liver, minimal (% not reported)/None | Renal (87), Feces (13)/ Renal (90) | 12.4/6.2 |
| Sitagliptin and simvastatin | 87/not reported | 38/95 | Liver, minimal (% not reported)/ Liver, extensive (% not reported) | Renal (87), Feces (13)/Renal (13), Feces (60) | 12.4/ not reported |

## V. Drug Interactions

Significant drug interactions with the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 5.

**Table 5. Significant Drug Interactions with the DPP-4 Inhibitors[20]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Sitagliptin and metformin | 1 | Iodine-containing radiopaque agents | Iodine-containing radiopaque agents can produce acute renal failure and decrease the clearance of sitagliptin/metformin. This may result in lactic acidosis. Sitagliptin/metformin should not be restarted until renal function returns to normal. |
| Simvastatin | 1 | Amiodarone | Inhibition of simvastatin metabolism is suspected. |
| Simvastatin | 1 | Azole antifungals | Azole antifungals may inhibit the first-pass hepatic metabolism of simvastatin. |
| Simvastatin | 1 | Cyclosporine | Decreased metabolism of simvastatin and increased bioavailability is suspected. |
| Simvastatin | 1 | Diltiazem | Possible inhibition of first-pass metabolism of simvastatin. |
| Simvastatin | 1 | Fibric acid derivatives | Unknown. |
| Simvastatin | 1 | Macrolide and related antibiotics | Inhibition of metabolism is suspected. |
| Simvastatin | 1 | Nefazodone | Inhibition of simvastatin metabolism is suspected. |
| Simvastatin | 1 | Nonnucleoside reverse transcriptase inhibitors | Nonnucleoside reverse transcriptase inhibitors may induce cytochrome P450 3A4 isoenzyme metabolism. |
| Simvastatin | 1 | Protease inhibitors | Inhibition of simvastatin first-pass metabolism in the gastrointestinal tract is suspected. |
| Simvastatin | 1 | Warfarin | Decreased S- and R-warfarin clearance by inhibition of cytochrome P450 2C9 and 3A4 isoenzymes metabolism, respectively. |
| Metformin | 2 | Ethanol | The hypoglycemic effects of sitagliptin/metformin may be increased by ethanol. The incidence of lactic acidosis may also be increased. |
| Simvastatin | 2 | Carbamazepine | Increased metabolism of simvastatin is suspected. |
| Simvastatin | 2 | Imatinib | Inhibition of simvastatin metabolism is suspected. |
| Simvastatin | 2 | Rifamycins | Rifamycins may induce first-pass metabolism and inhibit hepatic transported protein of simvastatin in the intestine and liver or may affect other intestinal transport mechanisms. |

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Simvastatin | 2 | Verapamil | Possible inhibition of first-pass metabolism of simvastatin. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

The most common adverse drug events reported with the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 6. The boxed warning for sitagliptin and metformin is listed in Table 7. There have been postmarketing reports of serious hypersensitivity reactions in patients taking DPP-4 inhibitors. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. There have also been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking DPP-4 inhibitors. Saxagliptin and sitagliptin have not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using sitagliptin.[1-8]

**Table 6. Adverse Drug Events (%) Reported with the DDP-4 Inhibitors[1-8]**

| Adverse Event | Single Entity Agents* | | | Combination Products* | | | |
|---|---|---|---|---|---|---|---|
| | Linagliptin | Saxagliptin | Sitagliptin | Linagliptin and Metformin† | Saxagliptin and Metformin† | Sitagliptin and Metformin† | Sitagliptin and Simvastatin† |
| Abdominal pain | - | 1.7 to 2.4 | 2.3 | - | - | 2.2 to 3.0 | - |
| Arthralgia | 5.7 | - | - | - | - | - | - |
| Back pain | 6.4 | - | - | - | - | - | - |
| Cough | 2.7 | - | - | ✔ | - | - | - |
| Decreased appetite | - | - | - | ✔ | - | - | - |
| Diarrhea | - | - | 3 | 6.3 | 5.8 to 9.9 | 2.4 to 7.5 | - |
| Fracture | - | ✔ ‡ | - | - | - | - | - |
| Gastroenteritis | - | 1.9 to 2.3 | - | - | - | - | - |
| Headache | 5.7 | 6.5 to 7.5 | 1.1 to 5.9 | - | 7.5 | 2.7 to 5.9 | - |
| Hyperlipidemia | 2.7 | - | - | - | - | - | - |
| Hypersensitivity | ✔ | 1.5 | ✔ | ✔ | - | ✔ | - |
| Hypertriglyceridemia | 2.4 | - | - | - | - | - | - |
| Hypoglycemia | 7.6 to 22.9 | 2.7 to 20.0 | 0.6 to 15.5 | 1.4 to 22.9 | 3.4 to 7.8 | 15.3 to 16.4 | - |
| Infection | - | ✔ | - | - | - | - | - |
| Lymphopenia | - | 0.5 to 1.5 | - | - | - | - | - |
| Myalgia | ✔ | - | - | - | - | - | - |
| Nasopharyngitis | 4.3 | 6.9 | 5.2 to 11.0 | 6.3 | 6.9 | 6.1 to 11.0 | - |
| Nausea | - | - | 1.4 | ✔ | - | 1.6 to 4.8 | - |
| Pancreatitis | ✔ | ✔ | ✔ | ✔ | - | - | - |
| Peripheral edema | - | 1.2 to 8.1 | 8.3 | - | - | 8.3 | - |
| Pruritis | - | - | - | ✔ | - | - | - |
| Rash | - | 0.2 to 0.3 | - | - | - | - | - |
| Sinusitis | - | 2.6 to 2.9 | - | - | - | - | - |
| Thrombocytopenia | - | ✔ | - | - | - | - | - |
| Upper respiratory tract infection | - | 7.7 | 4.5 to 15.5 | - | - | 5.5 to 6.2 | - |

| Adverse Event | Single Entity Agents* | | | Combination Products* | | | |
|---|---|---|---|---|---|---|---|
| | Linagliptin | Saxagliptin | Sitagliptin | Linagliptin and Metformin† | Saxagliptin and Metformin† | Sitagliptin and Metformin† | Sitagliptin and Simvastatin† |
| Urinary tract infection | - | 6.8 | - | - | - | - | - |
| Vomiting | - | 2.2 to 2.3 | - | ✔ | - | 1.1 to 2.2 | - |
| Weight gain | 2.3 | - | - | - | - | - | - |

-Event not reported or incidence <1%.
✔ Percent not specified.
*Administered as monotherapy or in combination with other antidiabetic agents.
†Adverse reactions for combination therapy only are reported.
‡ Incidence rate of 1 per 100 patient-years (pooled analysis of 2.5, 5, and 10 mg) compared to placebo (0.6 per 100 patient-years).

**Table 7. Boxed Warning for DPP-4 Inhibitor Combination Products Containing Metformin[3-7]**

| WARNING |
|---|
| Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected therapy should be discontinued and the patient hospitalized immediately. |

## VII. Dosing and Administration

The usual dosing regimens for the dipeptidyl peptidase-4 (DPP-4) inhibitors are listed in Table 8.

**Table 8. Usual Dosing Regimens for the DPP-4 Inhibitors[1-8]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Single-Entity Agents** | | | |
| Linagliptin | Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:<br>Tablet: 5 mg QD | Safety and efficacy in children have not been established. | Tablet:<br>5 mg |
| Saxagliptin | Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:<br>Tablet: 2.5 or 5 mg QD | Safety and efficacy in children have not been established. | Tablet:<br>2.5 mg<br>5 mg |
| Sitagliptin | Monotherapy or combination therapy as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes:<br>Tablet: 100 mg QD | Safety and efficacy in children have not been established. | Tablet:<br>25 mg<br>50 mg<br>100 mg |
| **Combination Products** | | | |
| Linagliptin and metformin | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both linagliptin and metformin is appropriate:<br>Tablet: initial, individualized on the basis of both effectiveness and tolerability; maximum, 2.5-1,000 mg BID | Safety and efficacy in children have not been established. | Tablet:<br>2.5-500 mg<br>2.5-850 mg<br>2.5-1,000 mg |
| Saxagliptin and metformin | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment with both saxagliptin and metformin is appropriate:<br>Extended-release tablet: initial, individualized on the basis of the patient's current regimen, effectiveness, and tolerability and administered QD; maximum, 5-2,000 mg/day | Safety and efficacy in children have not been established. | Extended-release tablet:<br>5-500 mg<br>2.5-1,000 mg<br>5-1,000 mg |
| Sitagliptin and metformin | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when treatment | Safety and efficacy in children have not been established. | Extended-release tablet:<br>50-500 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | with both sitagliptin and metformin or metformin extended-release is appropriate:<br>Extended-release tablet: initial, individualized based on the patient's current regimen and administered QD; maximum, 100-2,000 mg/day<br><br>Tablet: initial, individualized based on the patient's current regimen and administered BID; maximum, 100-2,000 mg/day | | 50-1,000 mg<br>100-1,000 mg<br><br>Tablet:<br>50-500 mg<br>50-1,000 mg |
| Sitagliptin and simvastatin | Patients for whom treatment with both sitagliptin and simvastatin is appropriate:<br>Tablet: initial, individualized based on the patient's current regimen and administered QD; usual starting dose is 100-40 mg QD | Safety and efficacy in children have not been established. | Tablet:<br>100-10 mg<br>100-20 mg<br>100-40 mg |

BID=twice daily, QD=once daily

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the dipeptidyl peptidase-4 (DPP-4) inhibitors are summarized in Table 9.

**Table 9. Comparative Clinical Trials with the DPP-4 Inhibitors**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Type 2 Diabetes – Monotherapy** | | | | |
| Rosenstock et al.[21] (2008)<br><br>Low-dose<br>Saxagliptin 2.5 to 40 mg QD<br><br>vs<br><br>placebo<br><br>High-dose<br>Saxagliptin100 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics ≥21 to ≤70 years of age with an $HbA_{1c}$ ≥6.8 to ≤9.7%, BMI ≤37 kg/m$^2$, and a screening fasting or random C-peptide >0.5 ng/mL | N=338<br><br>12 weeks (saxagliptin 2.5, 5, 10, 20, and 40 mg); 6 weeks (saxagliptin 100 mg) | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Analyses of each dose vs placebo for decreasing $HbA_{1c}$, FPG, and PPG at 60 minutes from baseline | Primary:<br>With low-dose saxagliptin, the test for log-linear trend across the treatment groups did not demonstrate a significant dose-response relationship in decreasing $HbA_{1c}$. Placebo-subtracted adjusted mean changes from baseline to week 12 with saxagliptin ranged from -0.45 to -0.63%, with no apparent significant dose-response relationship (P=0.9888).<br><br>Secondary:<br>After 12 weeks, $HbA_{1c}$ was significantly decreased with low-dose saxagliptin compared to placebo (all doses P<0.007), with similar and clinically meaningful decreases in $HbA_{1c}$ achieved with all doses of saxagliptin. Adjusted mean baseline decreases exceeded 0.70% with each saxagliptin dose compared to 0.27% with placebo. With high-dose saxagliptin, $HbA_{1c}$ was significantly decreased compared to placebo (-1.09 vs -0.36%; P value not reported).<br><br>With both low- and high-dose saxagliptin, decreases in FPG were evident after two weeks of treatment, and ranged from -11.0 to -22.0 mg/dL with low-dose saxagliptin compared to 3.0 mg/dL with placebo, and -26.3 mg/dL with high-dose saxagliptin compared to -3.3 mg/dL with placebo (P values not reported).<br><br>With low-dose saxagliptin decreases in PPG at 60 minutes during a liquid meal tolerance test ranged from -24.0 to -41.0 mg/dL compared to -1.0 mg/dL with placebo (P value not reported). With high-dose saxagliptin it was -45.0 mg/dL compared to -17.0 mg/dL with placebo (P value not reported). |
| Rosenstock et al (abstract).[22] (2009) | OL, PC, RCT<br><br>Treatment-naïve type 2 diabetics | N=401 (N=66 in the OL cohort) | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>In the main treatment cohort, saxagliptin significantly decreased $HbA_{1c}$ compared to placebo (-0.43, -0.46, and -0.54 vs 0.19% for placebo; all P<0.0001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Randomized cohort<br>Saxagliptin 2.5 to 10 mg QD<br><br>vs<br><br>placebo<br><br>Open-label cohort<br>Saxagliptin 10 mg QD<br><br>vs<br><br>placebo | with inadequate glycemic control, and an $HbA_{1c}$ ≥7.0 and ≤10.0% | 24 weeks | Secondary:<br>Change in baseline FPG and PPG, proportion of patients achieving an $HbA_{1c}$ <7.0% | Secondary:<br>Saxagliptin significantly decreased FPG compared to placebo (-15, -9, and -17 vs 6 mg/dL; P=0.0002, P=0.0074, and P<0.0001).<br><br>The decrease in PPG AUC with saxagliptin 2.5 (-6,868 [mg/minute]/[dL], 5 (-6,896 [mg/minute]/[dL], and 10 mg (-8,804 [mg/minute]/[dL] compared to placebo (-647 [mg/minute]/[dL] was only significant with saxagliptin 5 (P=0.0002) and 10 mg (P<0.0001).<br><br>Greater proportions of patients receiving saxagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (35 [P value not significant], 38 [P=0.0443], and 41 [P=0.0133] vs 24%).<br><br>Decreases in $HbA_{1c}$, FPG, and PPG AUC were observed in the OL cohort. |
| Aschner et al.[23] (2006)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>sitagliptin 200 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Type 2 diabetics 18 to 75 years of age, either receiving or naïve to oral antihyperglycemic agents, and an $HbA_{1c}$ 8.0% | N=741<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, PPG, fasting insulin, proinsulin, fasting lipids, β cell function, and insulin resistance<br><br>Secondary:<br>Safety and tolerability | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo (100 mg treatment difference, -0.79% [95% CI, -0.96 to -0.62] and 200 mg treatment difference, -0.94% [95% CI, -1.11 to -0.77]; a significantly greater proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (41 and 45 vs 17%; P<0.001 for both).<br><br>Sitagliptin significantly decreased FPG compared to placebo (100 mg treatment difference, -17.1 mg/dL and 200 mg treatment difference, -21.3 mg/dL; P<0.001 for both).<br><br>Sitagliptin significantly reduced two-hour PPG compared to placebo (-48.9 and -56.3 vs -2.2 mg/dL; P<0.001 for both).<br><br>There were no significant effects on fasting insulin and proinsulin with either treatment.<br><br>Sitagliptin also had no significant effects on fasting lipids.<br><br>HOMA-B was significantly increased and the proinsulin:insulin ratio was |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | significantly decreased with sitagliptin compared to placebo, indicating improved β cell function (P≤0.001 and P≤0.01, respectively).<br><br>Secondary:<br>There were fewer sitagliptin-treated patients compared to placebo-treated patients that required rescue therapy (8.8 and 4.8 vs 20.6%; P<0.001). No meaningful differences in clinical adverse effects were noted between the two treatments. The incidence of hypoglycemia was similar among the two treatments. Both doses of sitagliptin were well tolerated. |
| Hanefeld et al.[24] (2007)<br><br>Sitagliptin 25 mg QD<br><br>vs<br><br>sitagliptin 50 mg QD<br><br>vs<br><br>sitagliptin 50 mg BID<br><br>vs<br><br>sitagliptin 100 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 23 to 74 years of age and an $HbA_{1c}$ 7.6 to 7.8% | N=555<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, mean daily glucose, HOMA-B, QUICKI, and HOMA-IR<br><br>Secondary:<br>Adverse events, body weight | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ by -0.39 to -0.56% compared to placebo (P<0.05).<br><br>Sitagliptin significantly decreased FPG by -11.0 to -17.2 mg/dL compared to placebo (P<0.05), and the largest decrease was achieved with sitagliptin 100 mg QD.<br><br>Sitagliptin significantly improved mean daily glucose (-14.0 to -22.6 mg/dL; P<0.05).<br><br>HOMA-B was significantly increased (11.3 to 15.2; P<0.05) with sitagliptin, whereas there was no significant changes in QUICKI and HOMA-IR with sitagliptin compared to placebo.<br><br>Secondary:<br>Overall, there was a low frequency of hypoglycemia observed with sitagliptin.<br><br>There was no change in body weight observed with any treatment. |
| Raz et al.[25] (2006)<br><br>Sitagliptin 100 mg | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 | N=521<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>Sitagliptin (100 mg, -0.60% [95% CI, -0.82 to -0.39] and 200 mg, -0.48% [95% CI, -0.70 to -0.26]) significantly decreased $HbA_{1c}$ compared to placebo (P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| QD<br><br>vs<br><br>sitagliptin 200 mg QD<br><br>vs<br><br>placebo | to 75 years of age with an $HbA_{1c}$ 7.0 to 10.0% | | Secondary:<br>Change in baseline FPG, fasting insulin, proinsulin, and lipids; safety and tolerability | Secondary:<br>Sitagliptin (100 mg, -1.1 mmol/L [95% CI, -1.7 to -0.5] and 200 mg, -0.9 mmol/L [95% CI, -1.5 to -0.3]) significantly decreased FPG compared to placebo (P<0.001).<br><br>There were no significant effects on fasting insulin, proinsulin, or fasting lipids with either treatment.<br><br>Rescue therapy was required for 8.8, 11.7, and 17.3% of patients receiving sitagliptin 100 mg, sitagliptin 200 mg, and placebo (P value not reported). Treatment with sitagliptin was well tolerated, and no significant differences between treatments in the incidence of adverse effects were observed. The incidence of hypoglycemia and gastrointestinal side effects was similar between the two treatments. |
| Nonaka et al.[26] (2007)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Japanese patients with type 2 diabetics, $HbA_{1c}$ ≥6.5 to <10.0%, and FPG ≥126 to ≤240 mg/dL | N=151<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, PPG, body weight; adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>Sitagliptin (-0.65%; 95% CI, -0.80 to -0.50) significantly decreased $HbA_{1c}$ compared to placebo (0.41%; 95% CI, 0.26 to 0.56; treatment difference, -1.05%; 95% CI, -1.27 to -0.84; P <0.001). A significantly greater proportion of patients receiving sitagliptin achieved $HbA_{1c}$ <7.0% compared to patients receiving placebo (P<0.001).<br><br>Sitagliptin (-22.5 mg/dL; 95% CI, -28.0 to -17.0) significantly decreased FPG compared to placebo (9.4 mg/dL; 95% CI, 3.9 to 14.9; treatment difference, -31.9 mg/dL; 95% CI, -39.7 to -24.1; P<0.001).<br><br>Sitagliptin (-69.3 mg/dL; 95% CI, -85.3 to -53.4) significantly decreased PPG compared to placebo (12.0 mg/dL; 95% CI, -6.5 to 30.5; treatment difference, -81.3 mg/dL; 95% CI, -105.8 to -56.9; P<0.001).<br><br>Body weight was unchanged compared to baseline with sitagliptin (-0.1 kg), but significantly (P<0.01) different compared to placebo (-0.7 kg).<br><br>No notable difference in adverse events, including hypoglycemia, was observed between the two treatments.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Not reported |
| Scott et al.[27] (2007)<br><br>Sitagliptin 5 mg BID<br><br>vs<br><br>sitagliptin 12.5 mg BID<br><br>vs<br><br>sitagliptin 25 mg BID<br><br>vs<br><br>sitagliptin 50 mg BID<br><br>vs<br><br>glipizide 5 to 20 mg daily<br><br>vs<br><br>placebo | AC, DB, PC, RCT<br><br>Type 2 diabetics 21 to 75 years of age, inadequately controlled ($HbA_{1c}$ 7.9%) with diet and exercise | N=743<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, mean daily glucose, and body weight; adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>Sitagliptin (-0.38 to -0.77%) significantly decreased $HbA_{1c}$ compared to placebo (P<0.001). Sitagliptin 50 mg achieved the greatest decrease. The placebo subtracted difference in $HbA_{1c}$ of glipizide was -1.00%.<br><br>Sitagliptin significantly decreased FPG and mean daily glucose compared to placebo (P values not reported).<br><br>There was no difference between sitagliptin and placebo with changes in body weight. Glipizide resulted in a modest weight gain compared to placebo (P value not reported).<br><br>The incidence of hypoglycemia was highest with glipizide (17%) compared to placebo (2%) and sitagliptin (0 to 4%, not dose-dependent).<br><br>Secondary:<br>Not reported |
| Chan et al.[28] (2008)<br><br><u>Phase I</u><br>Sitagliptin 25 to 50 mg QD | DB, PC, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes, baseline $HbA_{1c}$ of 6.5 to 10.0%, and renal | N=91<br><br>54 weeks (Phase I was 12 weeks; Phase II was 42 weeks) | Primary:<br>Safety and tolerability<br><br>Secondary:<br>Efficacy | Primary:<br>Adverse events were similar among patients receiving sitagliptin and placebo/glipizide, including serious adverse events (30.8 and 38.5%, respectively), drug-related serious adverse events (1.5 and 0.0%, respectively), and adverse events leading to discontinuation.<br><br>Incidences of adverse events by body systems and specific clinical adverse |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>placebo<br><br><u>Phase II</u><br>Sitagliptin 25 to 50 mg daily and placebo<br><br>vs<br><br>glipizide 2.5 to 20 mg daily and placebo | insufficiency | | | events were also similar between the sitagliptin and placebo/glipizide groups, with the exception of hypoglycemia and anemia. Hypoglycemia occurred in 4.6% of patients receiving sitagliptin and 23.1% of patients receiving placebo/glipizide. Anemia occurred in 3.1% of patients receiving sitagliptin and 15.4% of patients receiving placebo/glipizide.<br><br>There was a higher incidence of MI (4.6 and 0.0%) and heart failure (7.7 and 3.8%) in the sitagliptin group compared to the placebo/glipizide group, respectively. The number of patients experiencing cardiovascular events per 100 patient-years was similar between groups.<br><br>There were six deaths (7.7%) in the sitagliptin group and one death (3.8%) in the placebo/glipizide group. This represents an overall mortality rate of 7.3 deaths per 100 patient-years, with 8.8 and 4.0 deaths per 100 patient-years in the sitagliptin and placebo/glipizide groups, respectively.<br><br>No clinically meaningful differences were observed for laboratory safety measures, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase, uric acid, electrolytes, white blood cell count or absolute neutrophil count between groups.<br><br>At week 54, the mean change from baseline in serum creatinine for patients with moderate renal insufficiency was -0.02 and 0.69 mg/dL in the sitagliptin and placebo/glipizide groups, respectively.<br><br>At week 54, small (2 mm Hg) mean decreases in systolic, diastolic and mean arterial BPs were observed for patients on sitagliptin compared to those on placebo/glipizide.<br><br>At week 54, there was a small mean decrease in body weight from baseline in the sitagliptin group (-0.9 kg) compared with no mean change in the placebo/glipizide group (0.0 kg).<br><br>Secondary:<br>At week 12, the mean change from baseline in $HbA_{1c}$ was -0.6% (95% CI, -0.8 to -0.4%) in the sitagliptin group compared with -0.2% (95% CI, -0.4 to 0.1%) in the placebo group |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | At week 12, the mean change from baseline in FPG was -25.5 mg/dL (95% CI, -38.2 to -12.8 mg/dL) with sitagliptin and -3.0 mg/dl (95% CI, -15.7 to 9.6) with placebo.<br><br>At week 54, the mean and least squares mean change from baseline in $HbA_{1c}$ with sitagliptin was -0.7% in the prespecified analysis and in the ANCOVA analysis. The mean and least squares mean changes from baseline were -1.0 and -0.8%, respectively in the placebo/glipizide group. Between-group testing for efficacy was not performed at the week 54 time point.<br><br>At week 54, the mean percent changes in lipids were as follows for sitagliptin: TC (+4.3%; 95% CI, -1.5 to 10.1), LDL-C (+11.9%; 95% CI, 1.6 to 22.2), and non-HDL-C (+7.1%; -1.2 to 15.3), TGs (-0.7%; 95% CI, -13 to 11.5), and HDL-C (+0.9%; 95% CI, -5.9 to 7.7). The mean percent changes in lipids in the placebo/glipizide group were as follows: TC (-0.2%; 95% CI, -10.5 to 10.0), LDL-C (3.3%; 95% CI, -8.6 to 15.2), non-HDL-C (-1.6%; 95% CI, -13.7 to 10.5), TG (+0.9%; 95% CI, -27.5 to 29.3), and HDL-C (+6.6%; 95% CI, -5 to 18.2). |
| DeFronzo et al.[29] (2008)<br><br>Sitagliptin 100 mg QD for 2 weeks<br><br>vs<br><br>exenatide 5 µg SC BID for 1 week, then 10 µg SC BID for 1 week | DB, MC, RCT, XO<br><br>Patients 18 to 70 years of age with type 2 diabetes who were treated with a stable regimen of metformin, $HbA_{1c}$ 7.0 to 11.0%, FPG <280 mg/dL, and BMI 25 to 45 kg/m$^2$ | N=95<br><br>4 weeks | Primary:<br>2-hour PPG<br><br>Secondary:<br>Postprandial insulin, glucagon, active GLP-1 and TG concentrations, and safety | Primary:<br>The 2-hour PPG concentration (least square mean) was lower for exenatide compared to sitagliptin (133 vs 208 mg/dL; P<0.0001). In the intent-to-treat population, the 2-hour PPG concentration was lower with exenatide compared to sitagliptin (166 vs 210 mg/dL, respectively; P<0.0001).<br><br>The change in 2-hour PPG concentration (least square mean) from baseline was -112 mg/dL for exenatide compared to -37 mg/dL for sitagliptin (P<0.0001).<br><br>FPG was similar following treatment with exenatide (-15 mg/dL) and sitagliptin (-19 mg/dL; P=0.3234).<br><br>Following crossover to the alternate therapy, patients switched from exenatide to sitagliptin experienced an increase in mean 2-hour PPG +73 mg/dL. Patients switched from sitagliptin to exenatide treatment |

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| | | | | experienced a reduction in the mean 2-hour PPG concentration -76 mg/dL.<br><br>Secondary:<br>The acute insulin response was greater for exenatide compared to sitagliptin (P=0.0017).<br><br>Both exenatide and sitagliptin reduced the mean postprandial plasma glucagon concentration compared to baseline; however, the reduction was greater with exenatide compared to sitagliptin (P=0.0011).<br><br>Both exenatide and sitagliptin both reduced mean postprandial TG concentrations compared to baseline; however, the decrease was greater with exenatide compared to sitagliptin (P=0.0118).<br><br>Exenatide reduced the rate of gastric emptying compared to baseline and to sitagliptin (P<0.0001). Sitagliptin had no effect on gastric emptying).<br><br>Adverse events with exenatide and sitagliptin were mild-to-moderate. The most common adverse events were gastrointestinal with both treatments. Nausea was experienced by 34% of patients treated with exenatide and 12% of patients treated with sitagliptin. Vomiting was experienced by 24% of patients treated with exenatide and 3% of patients treated with sitagliptin. No serious treatment-emergent adverse events were reported during the study. |
| Aschner et al.[30] (2010)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>metformin 1,000 mg BID | AC, DB, RCT<br><br>Patients 18 to 78 years of age with type 2 diabetes mellitus who were treatment naïve with an $HbA_{1c}$ 6.5 to 9.0% | N=1,050<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Proportions of patients with $HbA_{1c}$ <7.0% or <6.5%, change in FPG, fasting serum insulin, fasting serum proinsulin, and lipid | Primary:<br>In the per protocol population, the change in $HbA_{1c}$ (least square mean) from baseline at week 24 was −0.43% in the sitagliptin group and −0.57% in the metformin group (difference, 0.14%; 95% CI, 0.06 to 0.21), which demonstrated the non-inferiority of sitagliptin to metformin.<br><br>In the full analysis set, the $HbA_{1c}$ change from baseline at week 24 was −0.38% (95% CI, −0.43 to −0.32) in the sitagliptin group and −0.55% (95% CI, –0.61 to −0.50) in the metformin group (difference, 0.18%; 95% CI, 0.10 to 0.25), which demonstrated the non-inferiority of sitagliptin to metformin.<br><br>Secondary: |

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| | | | parameters | The proportion of patients with an $HbA_{1c}$ <7.0% at week 24 was greater with metformin (76%) compared with sitagliptin (69%; difference, -7.1%; 95% CI, −12.9 to −1.2).<br><br>The proportion of patients with an $HbA_{1c}$ <6.5% was not statistically different between the metformin (39%) and sitagliptin (34%) groups (difference, −5.6%; 95% CI, −11.8 to 0.8).<br><br>The change from baseline in FPG was greater with metformin (–19.4 mg/dl compared with sitagliptin (–11.5 mg/dL).<br><br>The reduction in fasting proinsulin was greater in the metformin group, which resulted in a larger reduction in the proinsulin/insulin ratio at week 24.<br><br>Both treatments produced similar increases in β-cell function and reductions in insulin resistance over 24 weeks.<br><br>HDL-C was improved with both treatments. TGs were slightly reduced with sitagliptin. Small increases in TC were observed for each group, with a slightly greater increase for sitagliptin. Modest increases in LDL-C and non-HDL-C were observed with sitagliptin, but not metformin over 24 weeks.<br><br>The incidence of drug-related adverse events was lower in the sitagliptin group than in the metformin group. The incidence of gastrointestinal adverse events overall was lower in the sitagliptin group compared with the metformin group (11.6 vs 20.7%, respectively). Hypoglycemia occurred at a low rate in both groups (1.7% with sitagliptin and 3.3% with metformin; P=0.116). Body weight was reduced from baseline in both the sitagliptin (−0.6 kg) and metformin (−1.9 kg; P<0.001). |
| Russell-Jones et al. (2012)[31]<br>DRUATION-4<br><br>Exenatide ER 2 mg SC once | DB, DD, MC, PG, RCT<br><br>Drug-naïve (patients excluded if treated with any | N=820<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of | Primary:<br>Decreases in $HbA_{1c}$ were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The $HbA_{1c}$ at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, |

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| weekly<br><br>vs<br><br>metformin 2,000 mg/day<br><br>vs<br><br>pioglitazone 45 mg/day<br><br>vs<br><br>sitagliptin 100 mg/day | antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with $HbA_{1c}$ 7.1 to 11.0%, BMI 23 to 45 kg/m$^2$, and stable weight | | patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported QOL | and sitagliptin, respectively.<br><br>Secondary:<br>Similar proportions of patients receiving exenatide ER and metformin achieved $HbA_{1c}$ <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved $HbA_{1c}$ <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001).<br><br>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26).<br><br>Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.<br><br>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892).<br><br>No clinically significant changes in serum lipids were observed with any treatment.<br><br>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329).<br><br>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients |

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| | | | | receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.<br><br>All treatments resulted in improvements in perceived treatment satisfaction, weight-related QOL, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported). |
| Monami et al.[32] (2011)<br><br>DPP-4 inhibitors (linagliptin, alogliptin*, sitagliptin, saxagliptin, vildagliptin*)<br><br>vs<br><br>placebo or active comparator (oral hypoglycemic agents and/or insulin) | MA (53 trials)<br><br>Patients with type 2 diabetes who were receiving a DPP-4 inhibitor | N=33,881<br><br>≥24 weeks | Primary:<br>Incidence of cancer<br><br>Secondary:<br>Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events | Primary:<br>There were 176 cases of cancer (107 and 69 in patients receiving DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90).<br><br>Secondary:<br>The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55).<br><br>The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively). |

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| | | | | There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006). |
| Fakhoury et al.[33] (2010)<br><br>Incretin-based therapies (exenatide, liraglutide, vildagliptin*, and sitagliptin)<br><br>vs<br><br>placebo | MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin)<br><br>Type 2 diabetics ≥18 years of age | N=Not reported<br><br>Duration varied (4 to 52 weeks | Primary:<br>Change in baseline $HbA_{1c}$ and weight, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease $HbA_{1c}$ compared to placebo.<br><br>Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline $HbA_{1c}$. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant.<br><br>There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; P<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; P=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide.<br><br>Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; P=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; P=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; P=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; P=0.050).<br><br>Secondary:<br>Not reported |

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| Amori et al.[34] (2007)<br><br>Incretin therapy (exenatide, liraglutide*, sitagliptin and vildagliptin*)<br><br>vs<br><br>non-incretin-based therapy (placebo or hypoglycemic agent) | MA (29 RCTs)<br><br>Type 2 diabetics | N=12,996<br><br>Duration varied (12 to 52 weeks) | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, proportion of patients achieving an $HbA_{1c}$ <7.0% | Primary:<br>Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in $HbA_{1c}$ favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81).<br><br>Specifically, no difference in the $HbA_{1c}$ was found in OL, non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar $HbA_{1c}$ efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported).<br><br>Secondary:<br>Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21).<br><br>Exenatide-treated patients were more likely to achieve an $HbA_{1c}$ <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in NI trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported. |
| Shyangdan et al.[35] (2011)<br><br>GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)<br><br>vs<br><br>non-GLP-1 | MA (RCTs)<br><br>Type 2 diabetics ≥18 years of age | N=not reported<br><br>8 to 26 weeks | Primary:<br>Change in baseline $HbA_{1c}$, incidence of hypoglycemia, weight change<br><br>Secondary:<br>Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function | Primary:<br>Change in baseline $HbA_{1c}$<br>Exenatide ER significantly decreased $HbA_{1c}$ compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an $HbA_{1c}$ <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an $HbA_{1c}$ <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).<br><br>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased $HbA_{1c}$ (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; |

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| receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas) | | | | P<0.05). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in $HbA_{1c}$ compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).<br><br>Compared to placebo, liraglutide 1.8 mg significantly decreased an $HbA_{1c}$ (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in $HbA_{1c}$ compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).<br><br>Liraglutide decreased $HbA_{1c}$ to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported). |

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| | | | | Liraglutide 1.2 mg was associated with a non-significant increase in $HbA_{1c}$ compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an $HbA_{1c}$ <7.0% compared to the 1.8 mg dose (P=0.92).<br><br>Incidence of hypoglycemia<br>The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).<br><br>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).<br><br>Weight loss<br>Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).<br><br>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported). |

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| | | | | Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).<br><br>Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).<br><br>Secondary:<br>Data on mortality and morbidity were not reported for any treatment.<br><br>QOL<br>Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.<br><br>Data for liraglutide were not reported.<br><br>Safety<br>Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).<br><br>Compared to placebo, withdrawals due to adverse events were between 5 |

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| | | | | and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.<br><br>BP<br>There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.<br><br>FPG<br>There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).<br><br>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). |

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| | | | | PPG<br>There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).<br><br>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable.<br><br>Lipid profile<br>TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.<br><br>β cell function<br>Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio. |
| Pinelli et al.[36] | MA, SR (5 RCTs) | N=not | Primary: | Primary: |

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| (2011)<br><br>GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*)<br><br>vs<br><br>exenatide and sitagliptin | Adult type 2 diabetics | reported<br><br>Duration varied (not reported) | Change in baseline $HbA_{1c}$, FPG, PPG, weight, BP, and lipid profile; safety<br><br>Secondary:<br>Not reported | Pooled analysis demonstrates modest decreases in $HbA_{1c}$ favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve $HbA_{1c}$ <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31).<br><br>Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04).<br><br>In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; P=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast (treatment difference, -24 mg/dL; P<0.0001) and dinner (-18 mg/dL; P=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (P<0.05).<br><br>Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44).<br><br>In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; P=0.006), but results were not significant in the three other trials (P values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; P=0.02). Between-group differences were not significant in the other three trials (P values not reported).<br><br>Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; P value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; |

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| | | | | P=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; P=0.05).<br><br>No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritus in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment.<br><br>Secondary:<br>Not reported |
| **Type 2 Diabetes – Combination Therapy** | | | | |
| Del Prato et al.[37] (2011)<br><br>Linagliptin 5 mg/day<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m$^2$, and either treatment-naïve or had previously received 1 oral antidiabetic agent | N=503<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving an $HbA_{1c}$ <7.0 or <6.5%, change in baseline $HbA_{1c}$ by visit over time, | Primary:<br>Adjusted mean differences of the change in $HbA_{1c}$ significantly favored linagliptin compared to placebo (-0.69%; P<0.0001).<br><br>Secondary:<br>The proportion of patients with a baseline $HbA_{1c}$ ≥7.0% who achieved an $HbA_{1c}$ <7.0% receiving linagliptin and placebo were 25.2 vs 11.6% (OR, 2.9; P=0.0006).<br><br>The difference between linagliptin and placebo in $HbA_{1c}$ decreases from baseline increased over time and favored linagliptin (-0.46% at week six to |

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| | (excluding TZDs) | | proportion of patients with an $HbA_{1c}$ decrease ≥0.5%, change in baseline FPG, and two-hour PPG, safety | -0.69% at week 24; P<0.0001 for all).<br><br>The proportion of patients who achieved an $HbA_{1c}$ decrease ≥0.5% was 47.1 vs 19.0% with linagliptin and placebo (OR, 4.2; P<0.0001).<br><br>Adjusted mean differences of the decrease in FPG significantly favored linagliptin compared to placebo (-1.3 mmol/L; P<0.0001).<br><br>Adjusted mean differences of the decrease in two-hour PPG significantly favored linagliptin compared to placebo (-3.2 mmol/L; P<0.0001).<br><br>Linagliptin was well tolerated. In the total population, 6.6% of patients discontinued treatment prematurely, most frequently due to adverse events (1.8%) or a refusal to continue medication (2.0%). A greater proportion of patients receiving placebo reported at least one adverse event (58.7 vs 52.4%) or serious adverse event (4.2 vs 3.0%). Hyperglycemia was the most frequently reported adverse event (8.6 vs 22.8%). Other more commonly reported adverse events with linagliptin included headache (2.7 vs 1.2%), hypertension (3.6 vs 1.2%), and back pain (2.7 vs 1.8%). No clinically significant findings emerged regarding laboratory analyses or vital signs. |
| Taskinen et al.[38] (2011)<br><br>Linagliptin 5 mg/day<br><br>vs<br><br>placebo<br><br>All patients also received metformin ≥1,500 mg/day. | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 80 years of age with BMI ≤40 $kg/m^2$, who had inadequate glycemic control on metformin ≥1,500 mg/day ($HbA_{1c}$ 7.0 to 10.0%) or metformin in combination with ≤1 other oral antidiabetic agent | N=701<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, two-hour PPG, body weight, and β cell function; change in baseline $HbA_{1c}$ and FPG over time; proportion of patients achieving an $HbA_{1c}$ <7.0 and <6.5%; proportion | Primary:<br>Linagliptin decreased $HbA_{1c}$ by -0.49% compared to 0.15% with placebo (treatment difference, -0.64%; 95% CI, -0.78 to -0.50; P<0.0001).<br><br>Secondary:<br>Linagliptin significantly decreased FPG compared to placebo (-0.6 vs 0.6 mmol/L; treatment difference, -1.2 mmol/L; P<0.0001).<br><br>Linagliptin significantly decreased PPG compared to placebo (-2.7 vs 1.0 mmol/L; treatment difference, -3.7 mmol/L; P<0.0001).<br><br>Neither treatment was associated with a significant change in body weight (-0.4 vs -0.5 kg; P value not reported).<br><br>HOMA-B demonstrated a clinically relevant difference between treatments in adjusted mean change from baseline at 24 weeks in favor of |

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| | ($HbA_{1c}$ 6.5 to 9.0%) for ≥10 weeks prior to trial entry | | of patients with an $HbA_{1c}$ decrease ≥0.5%; proportion of patients who required rescue medication; safety | linagliptin of 11.9 (mU/L)/(mmol/L), for a relative change of 1.26 (mU/L)/(mmol/L) (P=0.0005).<br><br>The significant difference between the two treatments in decreases in $HbA_{1c}$ increased over time from six to 18 weeks (-0.43 to -0.65%), and then remained stable until trial end (-0.64%). Decreases in FPG over time were similar, with linagliptin-treated patients achieving decreases over time. The difference between the two treatments in terms of adjusted mean change from baseline in FPG increased overtime (-0.9 to -1.2 mmol/L; P<0.0001 for all).<br><br>Among patients with a baseline $HbA_{1c}$ ≥7.0%, 26.0 vs 9.0% of those receiving linagliptin and placebo achieved an $HbA_{1c}$ <7.0% (OR, 4.4; 95% CI, 2.4 to 8.0; P=0.0001). A significant difference was also observed in achieving $HbA_{1c}$ <6.5% for those with a baseline $HbA_{1c}$ ≥6.5% (10 vs 2%; OR, 5.5; 95% CI, 1.9 to 15.6; P=0.0016).<br><br>Fifty and 22% of patients receiving linagliptin and placebo achieved a reduction in $HbA_{1c}$ ≥0.5% at 24 weeks (OR, 3.8; 95% CI, 2.5 to 5.7; P<0.0001).<br><br>More than twice as many patients receiving placebo required rescue medication (19 vs 8%; OR, 0.28; P=0.0001).<br><br>Overall, linagliptin was well tolerated and adverse events occurred at a similar rate with both treatments. Most adverse events were mild or moderate in intensity. All hypoglycemic events were of mild intensity and assistance was not required by any patient. The incidence of treatment-related adverse events was slightly higher among placebo-treated patients (10.7 vs 6.9%). No clinically significant findings emerged regarding laboratory analyses or vital signs. |
| Owens et al.[39] (2011)<br><br>Linagliptin 5 mg QD | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics ≥18 to ≤80 years of age, BMI ≤40 | N=1,058<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of | Primary:<br>Linagliptin significantly decreased $HbA_{1c}$ compared to placebo (treatment difference, -0.62%; 95% CI, -0.73 to 0.50; P<0.0001).<br><br>Secondary:<br>A significantly greater proportion of patients with baseline $HbA_{1c}$ ≥7.0% |

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| vs<br><br>placebo<br><br>Patients were also receiving metformin and a sulfonylurea. | kg/m$^2$, and $HbA_{1c}$ ≥7.0 and ≤10.0% despite receiving metformin ≥1,500 mg/day and the maximum tolerated dose of a sulfonylurea | | patients achieving an $HbA_{1c}$ <6.5 or <7.0%; proportion of patients achieving an $HbA_{1c}$ decrease ≥0.5%; change in baseline FPG, fasting plasma insulin, HOMA-B, HOMA-IR, body weight, waist circumference, and lipid profile; use of rescue medication; safety | achieved an $HbA_{1c}$ <7.0% with linagliptin compared to placebo (29.2 vs 8.1%; P<0.0001).<br><br>The proportion of patients achieving an $HbA_{1c}$ decrease ≥0.5% was 58.2 and 30.2% with linagliptin and placebo (P value not reported).<br><br>Linagliptin significantly decreased FPG (treatment difference, -7.0 mmol/L; 95% CI, -1.0 to -0.4; P<0.0001).<br><br>Linagliptin significantly improved HOMA-B and HOMA-IR compared to placebo (P<0.001).<br><br>No significant changes in body weight or waist circumference were observed with either treatment.<br><br>Only placebo-treated patients experienced a meaningful decrease in TG (-12 mg/dL). Changes in TC, HDL-C, and LDL-C were similar between the two treatments.<br><br>Of the patients receiving linagliptin, 5.4% required rescue medication compared to 13.0% of placebo-treated patients. The likelihood of requiring rescue medication was approximately three times lower with linagliptin (OR, 0.361; P<0.0001).<br><br>Overall, 66.3 and 59.7% of patients receiving linagliptin and placebo experienced adverse events. The proportion of patients reporting severe adverse events was low with both treatments (2.4 vs 1.5%). Hypoglycemia was the most commonly reported adverse event (22.7 vs 14.8%). Symptomatic hypoglycemia was reported in 16.7 and 10.3% of patients. Hypoglycemia was generally mild or moderate, with severe hypoglycemia reported in 2.7 and 4.8% of patients. |
| Forst et al.[40] (2010)<br><br>Linagliptin 1, 5, or 10 mg/day | AC, DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 21 to 75 years of age with BMI 25 to 40 | N=333<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline | Primary:<br>Placebo corrected decreases in $HbA_{1c}$ were -0.40±0.14 (P=0.006), -4.40±0.14 (P<0.001), and -8.00±1.50% (P<0.001) with linagliptin 1, 5, and 10 mg, respectively. Treatment with glimepiride significantly decreased $HbA_{1c}$ compared to treatment with placebo -0.68% (P<0.0001). |

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| vs<br><br>placebo<br><br>vs<br><br>glimepiride (OL) 1 to 3 mg/day<br><br>Patients were also receiving metformin. | kg/m$^2$, who had inadequate glycemic control on metformin alone ($HbA_{1c}$ 7.5 to 10.0%) | | FPG and body weight, proportion of patients achieving an $HbA_{1c}$ ≤7.0%, proportion of patients with an $HbA_{1c}$ decrease ≥0.5%, safety | Secondary:<br>Decreases in FPG were significantly greater with all doses of linagliptin compared to placebo. The placebo corrected FPG decrease were -1.1 (P=0.0020), -1.9 (P<0.0001), and -1.6 mmol/L (P<0.0001) with linagliptin 1, 5, and 10 mg, respectively.<br><br>After 12 weeks a small decrease in body weight was observed with all doses of linagliptin (-0.15, -0.57, and -1.27 kg, respectively; P values not reported).<br><br>Only one (1.4%) patient receiving placebo achieved an $HbA_{1c}$ ≤7.0% compared to ten (approximately 15%), nine (approximately 15%), and 14 (21%) patients receiving linagliptin 1, 5, and 10 mg/day, respectively (P values not reported).<br><br>A greater proportion of patients receiving linagliptin achieved an $HbA_{1c}$ decrease ≥0.5% compared to patients receiving placebo (43.8 to 53.2 vs 12.9%; P value not reported). In addition, $HbA_{1c}$ decreased by ≥1.0% in 14.1, 27.4, 22.7, and 7.7% with linagliptin 1 mg, linagliptin 5 mg, linagliptin 10 mg, and placebo (P values not reported).<br><br>Linagliptin was well tolerated. The most commonly reported adverse events were considered to be of mild or moderate intensity; however, ten patients experienced severe adverse events. No episodes of hypoglycemia were reported. Three (4.6%) patients experienced hypoglycemia after dosing with glimepiride. |
| Haak et al.[41] (2012)<br><br>Linagliptin 5 mg QD<br><br>vs<br><br>metformin 500 mg BID | DB, MC, PC, RCT<br><br>Patients 18 to 80 years of age with type 2 diabetes who were treatment-naïve ($HbA_{1c}$ 7.5 to 11.0%) or who had received one other oral antidiabetic drug ($HbA_{1c}$ 7.0 to | N=791<br><br>24 weeks | Primary:<br>Change from baseline in $HbA_{1c}$ at week 24<br><br>Secondary:<br>Change from baseline in FPG, change from baseline in $HbA_{1c}$ and FPG over time, | Primary:<br>After 24 weeks, the mean change in $HbA_{1c}$ was 0.1% with placebo, -0.5% with linagliptin 5 mg QD, -0.6% with metformin 500 mg BID, -1.1% with metformin 1,000 mg BID, -1.2% with linagliptin plus metformin 500 mg, and -1.6% with linagliptin plus metformin 1,000 mg.<br><br>The adjusted placebo-corrected mean changes in $HbA_{1c}$ were -1.7% (95% CI, -2.0 to -1.4) for linagliptin plus metformin 1,000 mg; -1.3% (95% CI, -1.6 to -1.1) for linagliptin plus metformin 500 mg; -1.2% (95% CI, -1.5 to -0.9) for metformin 1,000 mg; -0.8% (95% CI, -1.0 to -0.5) for metformin 500 mg, and -0.6% (95% CI, -0.9 to -0.3) for linagliptin monotherapy |

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| vs<br><br>metformin 1,000 mg BID<br><br>vs<br><br>linagliptin 2.5 mg BID and metformin 500 mg BID<br><br>vs<br><br>linagliptin 2.5 mg BID and metformin 1,000 mg BID<br><br>vs<br><br>placebo | 10.5%) | | proportion of patients requiring rescue therapy after failing to achieve pre-specified glycemic targets or discontinuing because of lack of efficacy, safety | (P<0.0001 for all).<br><br>The mean treatment differences for linagliptin plus metformin 1,000 mg vs metformin and linagliptin monotherapy were -0.5% (95% CI, -0.7 to -0.3) and -1.1% (95% CI, -1.4 to -0.9), respectively. For linagliptin plus metformin 500 mg, the respective mean differences were -0.6% (95% CI, -0.8 to -0.4) and -0.8% (95% CI, -1.0 to -0.6; P<0.0001 for all).<br><br>Secondary:<br>The adjusted placebo-corrected mean changes in FPG from baseline were -3.3 mmol/L (95% CI, -4.0 to -2.6) and -2.4 mmol/L (95% CI, -3.1 to -1.7) in the linagliptin plus metformin 1,000 mg and linagliptin plus metformin 500 mg groups, respectively. This is compared to -2.3 mmol/L (95% CI, -3.0 to -1.7), -1.4 mmol/L (95% CI, -2.1 to -0.8) and -1.0 mmol/L (95% CI, -1.7 to -0.3) in the metformin 1,000 mg, metformin 500 mg, and linagliptin monotherapy groups, respectively (P<0.0001 for all).<br><br>The proportion of patients requiring rescue therapy for inadequate glycemic control at week 24 was lower in the combination therapy groups (linagliptin plus metformin 1,000 mg, 4.3%; linagliptin plus metformin 500 mg, 7.3%) compared to either monotherapy alone (metformin 1,000 mg, 8.0%; metformin 500 mg, 13.5%; linagliptin, 11.1%).<br><br>The proportion of patients reporting adverse events were comparable across the active treatment groups. |
| Gomis et al.[42] (2011)<br><br>Linagliptin 5 mg/day<br><br>vs<br><br>placebo<br><br>All patients were receiving | DB, DD, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 80 years of age with BMI ≤40 kg/m$^2$, who had inadequate glycemic control ($HbA_{1c}$ 7.5 to 11.0%) | N=389<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving an $HbA_{1c}$ <7.0%; proportion of patients with an $HbA_{1c}$ decrease ≥0.5%; change in | Primary:<br>Combination therapy significantly decreased $HbA_{1c}$ compared to placebo (-1.06±0.06 vs -0.56±0.09%; treatment difference, -0.51%; 95% CI, -0.71 to -0.30; P<0.0001).<br><br>Secondary:<br>The proportion of patients achieving an $HbA_{1c}$ <7.0% was significantly greater with combination therapy compared to placebo (42.9 vs 30.5%; OR, 2.1; 95% CI, 1.3 to 3.5; P=0.0051).<br><br>A significantly greater proportion of patients receiving combination therapy had ≥5.0% decrease in $HbA_{1c}$ compared to patients receiving |

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| pioglitazone 30 mg/day. | | | baseline $HbA_{1c}$ over time; change in baseline FPG, β cell function, and body weight; safety | placebo (75.0 vs 50.8%; OR, 3.8; 95% CI, 2.3 to 6.4; P<0.0001).<br><br>The placebo corrected difference in adjusted mean change from baseline in $HbA_{1c}$ increased over the first 12 weeks (reaching -0.5%), and remained constant until trial end. Combination therapy resulted in a larger decrease in non-adjusted $HbA_{1c}$ over time compared to placebo (P<0.0001 at each visit).<br><br>Combination therapy significantly decreased FPG compared to placebo (-1.8±0.1 vs -1.0±0.2 mmol/L; treatment difference, -0.8 mmol/L; P<0.0001).<br><br>There was no difference in decreases in HOMA-IR between the two treatments (-2.90 vs -2.58; treatment difference, -0.32; 95% CI, -0.77 to 0.13; P=0.16). Similar results were observed with HOMA-B (-2.17 vs -1.44; treatment difference, -0.73; 95% CI, -9.16 to 7.70; P=0.86).<br><br>Both treatments resulted in weight gain, with the increase being significantly greater with combination therapy (2.3 vs 1.2 kg; treatment difference, 1.1 kg; 95% CI, 0.2 to 2.0; P=0.014).<br><br>Overall, the proportion of patients who experienced at least one adverse event was similar with both treatments (52.5 vs 53.1%). Most adverse events were of mild to moderate intensity. Hypoglycemia occurred in 1.2 and 0.0% of patients receiving combination therapy and placebo, respectively. Laboratory analyses did not reveal any clinically significant findings. |
| Chacra et al.[43] (2010)<br><br>Saxagliptin 2.5 mg QD and glyburide 7.5 to 15 mg daily<br><br>vs<br><br>saxagliptin 5 mg | DB, MC, RCT<br><br>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.5 to ≤10.0%), on a submaximal sulfonylurea dose | N=768<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving | Primary:<br>Saxagliptin significantly decreased $HbA_{1c}$ compared to placebo (-0.54 and -0.64 vs 0.08%; P<0.0001 for both).<br><br>Secondary:<br>Saxagliptin significantly decreased FPG compared to placebo (2.5 mg; P=0.0218 and 5 mg; P=0.002).<br><br>Saxagliptin significantly decreased PPG $AUC_{0\text{-}3hr}$ compared to placebo (-4,296 and -5,000 vs 1,196 (mg/minute)/(dL); P<0.0001 for both). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| QD and glyburide 7.5 to 15 mg daily<br><br>vs<br><br>glyburide 2.5 to 15 mg daily and placebo | for ≥2 months before screening, fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | | an $HbA_{1c}$ <7.0%, safety | A significantly greater proportion of patients receiving saxagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (22.4 and 22.8 vs 9.1%; P<0.0001 for both).<br><br>Overall saxagliptin was well tolerated. The proportion of patients reporting any adverse event was similar across all treatments; with no evidence of a dose-response relationship. The proportion of patients reporting at least one adverse event and at least one treatment-related adverse event was 75.0 and 19.8, 72.3 and 21.3, and 76.8 and 14.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events were: 2.0, 4.0 and 3.7% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. Hypertension was reported in 3.6, 6.3, and 2.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo; however, mean SBP and DBP decreased with all treatments. There was no difference in the incidence of reported and confirmed hypoglycemic events with saxagliptin compared to placebo (P>0.05). Confirmed hypoglycemia occurred in 2.4, 0.8, and 0.7% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. |
| Barnett et al.[44] (2012)<br><br>Saxagliptin 5 mg QD<br><br>vs<br><br>placebo<br><br>All patients also received insulin alone or in combination with metformin. | DB, MC, RCT<br><br>Type 2 diabetics with inadequate glycemic control ($HbA_{1c}$ 7.5 to 11.0% on stable insulin therapy (30 to 150 U/day alone or in combination with metformin) for at least 8 weeks | N=455<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to week 24 (or rescue), PPG, FPG, body weight, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>Patients treated with saxagliptin had significantly greater reductions in adjusted mean $HbA_{1c}$ (difference, -0.41%; P<0.0001), PPG 180-minute AUC (-3829.8 mg/minute/dL; P=0.0011), and 120-minute PPG (-23.0 mg/dL; P=0.0016) at 24 weeks compared to placebo.<br><br>Treatment with saxagliptin resulted in similar reductions in $HbA_{1c}$ relative to placebo, irrespective of metformin treatment. At 24 weeks, difference in adjusted mean FPG for saxagliptin compared to placebo was -4.02 mg/dL (P=0.3958); 17.3 and 6.7% of patients in the saxagliptin and placebo groups, respectively, achieved $HbA_{1c}$ <7.0%.<br><br>Mean change from baseline in body weight at week 24 was 0.39 kg for saxagliptin and 0.18 kg for placebo. Hypoglycemia was reported in 18.4% and 19.9% of patients in the saxagliptin and placebo groups, respectively. Other adverse events reported in at least 5% of patients were urinary tract infection (5.9 vs 6.0%), influenza (3.0 vs 6.6%), and pain in extremity (1.6 vs6.0%). |

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| | | | | Secondary:<br>Not reported |
| Stenlöf et al.[45] (2010)<br><br>Saxagliptin 5 mg QD<br><br>vs<br><br>placebo<br><br>All patients also received metformin ER ≥1,500 mg/day. | DB, MC, PC, RCT<br><br>Type 2 diabetics with inadequate glycemic control ($HbA_{1c}$ 7.0 to 10.0%), and currently receiving stable doses of metformin IR or metformin ER (≥1,500 mg/day) as monotherapy for ≥8 weeks | N=93<br><br>4 weeks | Primary:<br>Change in baseline 24-hour mean weighted glucose<br><br>Secondary:<br>Change in baseline four-hour mean weighted PPG, two-hour PPG (both assessed after the evening meal), three-day average mean daily glucose, and two-day average FPG | Primary:<br>Saxagliptin significantly decreased 24-hour mean weighted glucose compared to placebo (-13.8 vs -3.0 mg/dL; P<0.0001).<br><br>Secondary:<br>Saxagliptin significantly decreased four-hour mean weighted PPG compared to placebo (-30.7 vs 0.4 mg/dL; P<0.0001). Similar results were observed with two-hour mean weighted PPG (-38.2 vs -2.8 mg/dL; P=0.0010).<br><br>Saxagliptin significantly decreased three-day average mean daily glucose compared placebo (-11.7 vs 7.0 mg/dL; P<0.0001).<br><br>Saxagliptin significantly decreased two-day average FPG compared to placebo (-10.8 vs 4.5 mg/dl; P=0.002). |
| DeFronzo et al.[46] (2009)<br><br>Saxagliptin 2.5 to 10 mg QD and metformin (existing therapy)<br><br>vs<br><br>metformin (existing therapy) and placebo | DB, PC, RCT<br><br>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.0 to ≤10.0%), receiving stable doses of metformin (≥1,500 to <2,550 mg/day) ≥8 weeks, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | N=743<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an $HbA_{1c}$<7.0% | Primary:<br>Saxagliptin significantly decreased $HbA_{1c}$ compared to placebo (-0.59, -0.69, and -0.58 vs 0.13%; P<0.0001 for all), with significance achieved after four weeks.<br><br>Secondary:<br>Saxagliptin significantly decreased FPG compared to placebo (-14.31, -22.03, and -20.50 vs 1.24 mg/dL; P<0.0001 for all). Similar results were observed with PPG $AUC_{0\text{-}3hr}$ (-8,891, -9,586, and -8,137 vs -3,291 [mg/minute]/[dL]; P<0.0001 for all).<br><br>A significantly greater proportion of patients achieved an $HbA_{1c}$ <7.0% with saxagliptin compared to placebo (37.1, 43.5, and 44.4 vs 16.6%; P<0.0001 for all). |
| Pfutzner et al.[47] (2011) | AC, DB, ES, MC, RCT | N=1,306 | Primary:<br>Change in baseline | Primary:<br>Decreases in $HbA_{1c}$ with saxagliptin 5 mg plus metformin were -2.31% |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Saxagliptin 5 and 10 mg QD plus metformin 500 mg/day<br><br>vs<br><br>saxagliptin 10 mg QD<br><br>vs<br><br>metformin 500 mg/day | Type 2 diabetics 18 to 77 years of age, $HbA_{1c}$ ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | 52 weeks (76 weeks total) | $HbA_{1c}$<br><br>Secondary:<br>Change in baseline body weight, proportion of patients achieving an $HbA_{1c}$ <7.0 and ≤6.5% | (95% CI -2.44 to -2.18) and -2.33% (95% CI -2.46 to -2.20) with saxagliptin 10 mg plus metformin compared to -1.55 (95% CI, -1.70 to -1.40) and -1.79% (95% CI, -1.93 to -1.65) with saxagliptin and metformin monotherapies, respectively; P<0.0001 for combination therapy vs monotherapy).<br><br>Secondary:<br>Decreases in body weight were -1.2 kg with saxagliptin 5 mg plus metformin, -0.7 kg with saxagliptin 10 mg plus metformin, -0.3 kg with saxagliptin, and -1.0 kg with metformin (P values not reported).<br><br>A greater proportion of patients achieved an $HbA_{1c}$ <7.0% with saxagliptin 5 mg plus metformin and saxagliptin 10 mg plus metformin compared to saxagliptin and metformin (51.5 and 50.5 vs 25.0 and 34.7%, respectively; P values not reported). Similar results were observed with $HbA_{1c}$ <6.5% (P values not reported). |
| Jadzinsky et al.[48] (2009)<br><br>Saxagliptin 5 mg QD plus metformin 500 to 2,000 mg daily<br><br>vs<br><br>saxagliptin 10 mg QD plus metformin 500 to 2,000 mg daily<br><br>vs<br><br>saxagliptin 10 mg QD<br><br>vs | AC, DB, MC, RCT<br><br>Type 2 diabetics 18 to 77 years of age, $HbA_{1c}$ ≥8.0 to ≤12.0%, fasting C-peptide concentration ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | N=1,306<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an $HbA_{1c}$ <7.0 and ≤6.5%, proportion of patients requiring rescue for failing to achieve prespecified glycemic targets or discontinuing for lack of efficacy at 24 weeks | Primary:<br>Combination therapy significantly decreased $HbA_{1c}$ compared to monotherapy with either saxagliptin or metformin (-2.5 and -2.5 vs -1.7 and -2.0%, respectively; P<0.0001 vs monotherapy for all).<br><br>Secondary:<br>Combination therapy significantly decreased FPG compared to monotherapy with either saxagliptin or metformin (P=0.0002 for saxagliptin 5 mg plus metformin vs saxagliptin and P<0.001 for saxagliptin 10 mg plus metformin vs saxagliptin and metformin). Similar results were observed for PPG $AUC_{0\text{-}3hr}$ (P<0.0001 for all vs monotherapy).<br><br>The proportion of patients achieving an $HbA_{1c}$ <7.0% was significantly greater with combination therapy compared to monotherapy with either agent (60.3 and 59.7 vs 32.2 and 41.1%; P<0.0001 for all vs monotherapy). Similar results were observed for $HbA_{1c}$ ≤6.5% (45.3 and 40.6 vs 20.3 and 29.0%; P<0.0001 for saxagliptin 5 mg plus metformin vs saxagliptin and metformin; P<0.0001 for saxagliptin 10 mg plus metformin vs saxagliptin, and P=0.0026 for saxagliptin 10 mg plus metformin vs metformin). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| metformin 500 to 2,000 mg daily | | | | At week 24, 7.5% of patients receiving saxagliptin 5 mg plus metformin and 21.2% of patients receiving saxagliptin 10 mg were discontinued or rescued for lack of glycemic control (P<0.0001). No significance was observed when saxagliptin 5 mg plus metformin was compared to metformin (P=0.2693). Similar results were observed with saxagliptin 10 mg plus metformin compared to either monotherapy (P<0.0001 vs saxagliptin 10 mg and P=0.0597 vs metformin). |
| Hollander et al.[49] (2009)<br><br>Saxagliptin 2.5 mg and TZD (existing therapy)<br><br>vs<br><br>saxagliptin 5 mg and TZD (existing therapy)<br><br>vs<br><br>TZD (existing therapy) and placebo | DB, MC, RCT<br><br>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.0 to ≤10.5%) receiving stable doses of TZD (pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day for ≥12 weeks), fasting C-peptide ≥0.3 nmol/L, and BMI ≤45 kg/m$^2$ | N=565<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an $HbA_{1c}$ <7.0% | Primary:<br>Saxagliptin significantly decreased $HbA_{1c}$ compared to placebo (saxagliptin 2.5 mg, -0.66%; treatment difference, -0.36%; P<0.0007 vs placebo and saxagliptin 5 mg, -0.94%; treatment difference, -0.63%; P<0.0001 vs placebo).<br><br>Secondary:<br>Saxagliptin significantly decreased FPG compared to placebo (saxagliptin 2.5 mg treatment difference, -0.8 mmol/L; P<0.0053 vs placebo and saxagliptin 5 mg treatment difference, -1.0 mmol/L; P=0.0005 vs placebo).<br><br>A significantly greater proportion of patients receiving saxagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (42.2 [P=0.0010] and 41.8 [P=0.0013] vs 25.6%).<br><br>Saxagliptin significantly decreased PPG $AUC_{0\text{-}3hr}$ compared to placebo (P<0.0001 for both). Similar results were observed with PPG $AUC_{0\text{-}2hr}$ (P<0.0001 for both).<br><br>Overall, saxagliptin was well tolerated. The proportion of patients experiencing any adverse effect was 68.0 vs 66.8%, with the highest frequency with saxagliptin 5 mg. The frequency of hypoglycemic events was similar between the two treatments (3.4 vs 3.8%). The most commonly reported adverse events were upper respiratory tract infection, peripheral edema, and headache. |
| Frederich et al.[50] (2010 ) | SR<br><br>Inadequately | N=4,607<br><br>16 to 116 | Primary:<br>Composite of cardiovascular | Primary:<br>There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Saxagliptin 2.5 to 10 mg QD<br><br>vs<br><br>glyburide, metformin, or placebo | controlled type 2 diabetics | weeks | events, cardiovascular death, MI, and stroke<br><br>Secondary:<br>Not reported | There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63).<br><br>Secondary:<br>Not reported |
| Scheen et al.[51] (2010)<br><br>Saxagliptin 5 mg QD<br><br>vs<br><br>sitagliptin 100 mg QD<br><br>Patients also received metformin. | AC, DB, MC, PG, RCT<br><br>Type 2 diabetics ≥18 years of age, with uncontrolled $HbA_{1c}$ (6.5 to 10.0%) despite monotherapy with a stable dose of metformin ≥1,500 mg for ≥8 weeks | N=801<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving an $HbA_{1c}$ ≤6.5%; proportion of patients with baseline $HbA_{1c}$ ≥7.0% achieving an $HbA_{1c}$ <7.0%; change in baseline FPG, insulin, C-peptide, proinsulin, and β cell function | Primary:<br>Saxagliptin was non-inferior to sitagliptin (-0.52 vs -0.62%). The adjusted mean decrease in $HbA_{1c}$ was 0.09% (95% CI, -0.01 to 0.20), with the upper limit for non-inferiority <0.3%.<br><br>Secondary:<br>A higher proportion of patients receiving sitagliptin achieved $HbA_{1c}$ ≤6.5% compared to patients receiving saxagliptin (29.1 vs 26.3%; P value not reported).<br><br>For patients with baseline $HbA_{1c}$ ≥7.0%, a non-significantly higher proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving saxagliptin (39.1 vs 33.0%; treatment difference, -6.1%; 95% CI, -13.8 to 1.6%).<br><br>Sitagliptin significantly decreased FPG compared to saxagliptin (-16.2 vs -10.8 mg/dL; treatment difference, -5.42 mg/dL; 95% CI, 1.37 to 9.47).<br><br>There were no apparent differences between the two treatments for the changes in fasting insulin, glucagon, proinsulin, or C-peptide. Similarly, the small improvement in β cell function did not differ between the two treatments. |
| Goke et al.[52] (2010)<br><br>Saxagliptin 5 mg/day<br><br>vs | DB, NI, RCT<br><br>Patients ≥18 years of age with type 2 diabetes with type 2 diabetes, $HbA_{1c}$ >6.5 to 10.0%, and | N=858<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Hypoglycemia, safety | Primary:<br>The per protocol analysis demonstrated non-inferiority of saxagliptin vs glipizide; adulated mean changes from baseline $HbA_{1c}$ were -0.74 vs -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05 to 0.16).<br><br>There was a significantly smaller risk in $HbA_{1c}$ (%/week) from week 24 to |

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| glipizide 5 mg/day, titrated up to 20 mg/day | inadequate glycemic control on metformin alone | | | 52 with saxagliptin vs glipizide (0.001 vs 0.004%; *P*=0.04) indicating a sustained glycemic effect beyond week 24.<br><br>Secondary:<br>Treatment with saxagliptin vs glipizide was associated with a significantly smaller proportion of patients with hypoglycemic events (3.0 vs 36.3%; *P*<0.0001) and a divergent impact on body weight (adjusted mean change from baseline, -1.1 vs 1.1 kg; *P*<0.0001).<br><br>Excluding hypoglycemic events, the proportion of patients reporting adverse events was smaller with glipizide (60.0 vs 56.7%); however, treatment-related adverse events were less common with saxagliptin (9.8 vs 31.2%), attributable to the higher frequency of hypoglycemia with glipizide. Discontinuation rates resulting from adverse events were similar (approximately 4%). |
| Harashima et al.[53] (2012)<br><br>Sitagliptin 100 mg QD<br><br>All patients received existing sulfonylurea therapy. | PRO, SA<br><br>Type 2 diabetics ≥20 years of age inadequately controlled on sulfonylureas, with or without metformin and/or α-glucosidase inhibitors, $HbA_{1c}$ ≥6.9%, no improvement in $HbA_{1c}$ ≥0.5% within 3 months, and a wish to diet and exercise to improve health | N=82<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Changes in BMI, BP, urinary albumin excretion, unresponsive rate, hypoglycemia | Primary:<br>Change in $HbA_{1c}$ was -0.80% (95% CI, -0.90 to -0.68; P<0.001).<br><br>Secondary:<br>Change in BMI, SBP, DBP, and urinary albumin excretion were -0.38 $kg/m^2$ (95% CI, -0.72 to -0.04; P<0.05), -6.7/-3.6 mm Hg (95% CI, -10.0 to -3.4/-4.8 to -2.4; P<0.001), and -43.2 mg/gCr (95% CI, -65.7 to -20.8; P<0.001), respectively.<br><br>The unresponsive rate was 6.1%.<br><br>Mild hypoglycemia was observed in three cases. |
| Brazg et al.[54] (2007)<br><br>Sitagliptin 50 mg | DB, PC, RCT, XO<br><br>Type 2 diabetics 25 to 75 years of age | N=28<br><br>8 weeks | Primary:<br>24-hour weighted mean glucose | Primary:<br>Sitagliptin (-32.8 mg/dL) significantly decreased 24-hour weighted mean glucose compared to placebo (P<0.05). |

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| BID<br><br>vs<br><br>placebo<br><br>All patients were receiving metformin ≥1,500 mg daily. | with inadequate glycemic control receiving metformin monotherapy, and an $HbA_{1c}$ of 6.5 to 9.6% | | Secondary:<br>Change in FPG, mean daily glucose, fructosamine, and β cell function; safety | Secondary:<br>Despite a carryover effect from Period 1 to 2, the combined Period 1 and 2 results for glycemic measurements were significant with sitagliptin compared to placebo. The Period 1 results were also compared between the groups, in consideration of any carryover.<br><br>Following Period 1, there were significant decreases in FPG of -20.3 mg/dL, mean daily glucose of -28 mg/dL, and fructosamine of -33.7 mmol/L with sitagliptin compared to placebo (P<0.05).<br><br>Sitagliptin significantly improved β cell function compared to placebo.<br><br>There was no difference in weight gain, gastrointestinal adverse events, and hypoglycemia between the two treatments. |
| Charbonnel et al.[55] (2006)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>placebo<br><br>All patients were receiving metformin ≥1,500 mg daily. | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 78 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.0 to ≤10.0%) on metformin monotherapy | N=701<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, PPG, insulin, C-peptide concentrations, β cell function, and lipid profile; safety | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo (treatment difference, -0.65%; P<0.001). A significantly greater proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% (47.0 vs 18.3%; P<0.001) and <6.5% (17.2 vs 4.9%; P<0.001) compared to patients receiving placebo.<br><br>Secondary:<br>Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -25.4 mg/dL; P<0.001). Similar results were observed with PPG (treatment difference, -50.6 mg/dL; P≤0.001).<br><br>Sitagliptin significantly increased fasting insulin (P<0.050) and fasting C-peptide (P<0.010) compared to placebo. There was observed improvement in fasting proinsulin:insulin ratio (P<0.010) and HOMA-B (P<0.001) consistent with improved β cell function with sitagliptin.<br><br>There were differences between the two treatments in changes in LDL-C.<br><br>There were no differences between two treatments in the incidences of overall or serious adverse reactions, rates of hypoglycemia, or gastrointestinal adverse events. A reduction in weight of 0.6 to 0.7 kg was observed with both treatment groups (P<0.050), but there was no |

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| | | | | difference between the two treatments (P=0.835). |
| Raz et al.[56] (2008)<br><br>Sitagliptin 100 mg daily plus metformin 1,500 to 2,550 mg daily (existing therapy)<br><br>vs<br><br>metformin 1,500 to 2,550 mg daily (existing therapy) plus placebo | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 78 years of age, $HbA_{1c}$ 7.0 to 10.0% receiving metformin or other oral antihyperglycemic agents as monotherapy or being treated with metformin in combination with other oral antihyperglycemic agents | N=190<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$ at 18 weeks<br><br>Secondary:<br>Change in baseline FPG at 18 weeks, two-hour PPG at 18 weeks, and $HbA_{1c}$ at 30 weeks; safety and tolerability | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo (treatment difference, -1.0%; 95% CI, -1.4 to -0.7; P<0.001). Numerically greater decreases in $HbA_{1c}$ were observed in patients with a higher baseline $HbA_{1c}$. A greater proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% at weeks 18 and 30 compared to patients receiving placebo (13.7 and 22.1 vs 3.3 and 3.3%; P values not reported).<br><br>Secondary:<br>Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -1.4 mmol/L; 95% CI, -2.1 to -0.7; P<0.001).<br><br>Sitagliptin significantly decreased two-hour PPG compared to placebo (treatment difference, -3.0 mmol/L; 95% CI, -4.2 to -1.9; P<0.001).<br><br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo at week 30 (treatment difference, -1.0%; 95% CI, -1.4 to -0.6; P<0.001).<br><br>The incidence of adverse events was similar with both treatments. No serious adverse events or discontinuations due to clinical adverse events were reported with sitagliptin. With placebo, there were six serious clinical adverse events that resulted in one death and two discontinuations. None of the adverse events were deemed to be drug-related. There were no differences between the two treatments in the incidences of hypoglycemia or gastrointestinal adverse events (abdominal pain, nausea, vomiting, and diarrhea). Over the 30 week period a small decrease in weight of 0.5 kg was observed with both treatments. |
| Goldstein et al.[57] (2007)<br><br>Sitagliptin 50 mg BID plus metformin 500 mg BID<br><br>vs | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 78 years of age and an $HbA_{1c}$ of 7.5 to 11.0% | N=1,091<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, | Primary:<br>Decreases in $HbA_{1c}$ were significant with all active treatments as compared to placebo and for combination therapy compared to monotherapy (P<0.001). There was an additive effect seen in the combination treatment groups. The proportion of patients achieving an $HbA_{1c}$ <7.0% was significantly greater with all active treatments compared to placebo (P<0.001).<br><br>Secondary: |

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| sitagliptin 50 mg BID plus metformin 1,000 mg BID<br><br>vs<br><br>sitagliptin 100 mg QD<br><br>vs<br><br>metformin 500 mg BID<br><br>vs<br><br>metformin 1,000 mg BID<br><br>vs<br><br>placebo | | | lipid profiles, β cell function, insulin resistance; adverse events | Significant decreases in FPG were achieved between combination therapy and monotherapy, and between all active treatments compared to placebo (P<0.001).<br><br>Data on fasting serum insulin and lipid profiles were not reported.<br><br>Combination therapy demonstrated an additive effect, as compared to monotherapy, with regards to improvements in β cell function.<br><br>HOMA-B increased with all active treatments compared to placebo (P<0.001). The combination therapy significantly increased HOMA-B compared to monotherapy (sitagliptin and low-dose metformin; P≤0.001).<br><br>Significant improvements in the proinsulin:insulin ratio observed with all active treatments compared to placebo (P<0.05). Differences between combination therapy and monotherapy were also significant (P<0.05).<br><br>The incidence of adverse events was similar between combination therapy and metformin. Gastrointestinal adverse events including diarrhea, nausea, abdominal pain, and vomiting were most frequently observed with metformin high-dose both as monotherapy and combination therapy. A low frequency of hypoglycemia was similar among all treatments (0.6 to 2.2%). No change in weight was observed with sitagliptin compared to all other active treatments, where there was a significant decrease in body weight (-0.6 to -1.3 kg; P<0.05) and placebo (-0.9 kg; P<0.01). |
| Reasner et al.[58] (2011)<br><br>Sitagliptin/ metformin 50/500 to 1,00 mg BID<br><br>vs<br><br>metformin 500 to 1,000 mg BID | DB, MC, PG, RCT<br><br>Treatment-naïve type 2 diabetics 18 to 78 years of age, and an $HbA_{1c}$ ≥7.5% | N=1,250<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving an $HbA_{1c}$ <7.0 and <6.5%, change in baseline FPG, proinsulin:insulin ratio, and β cell | Primary:<br>Combination therapy significantly decreased $HbA_{1c}$ compared to metformin (-2.4 vs -1.8%; P<0.001).<br><br>Secondary:<br>A significantly greater proportion of patients receiving combination therapy achieved an $HbA_{1c}$ <7.0% (49.2 vs 34.2%, respectively; P<0.001) and <6.5% (31.8 vs 16.0%, respectively; P<0.001) compared to patients receiving metformin.<br><br>Combination therapy significantly decreased FPG compared to metformin (-3.8 vs -3.0 mg/dL; P<0.001). |

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| | | | function | Combination therapy significantly decreased proinsulin:insulin ratio compared to metformin (-0.238 vs -0.186; P<0.05).<br><br>Combination therapy significantly improved β cell function compared to metformin (P<0.05). |
| Rosenstock et al.[59] (2006)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>placebo<br><br>All patients were receiving pioglitazone 30 or 45 mg QD. | DB, MC, PC, PG, RCT<br><br>Type 2 diabetics ≥18 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.0 to ≤10.0%) on pioglitazone monotherapy | N=353<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, fasting insulin, proinsulin, and lipid profiles; safety and tolerability | Primary:<br>Combination therapy (-0.70%; 95% CI, -0.85 to -0.54) significantly decreased $HbA_{1c}$ compared to placebo (P<0.001). A significantly greater proportion of patients receiving combination therapy achieved $HbA_{1c}$ <7.0% compared to patients receiving placebo (45 vs 23%; P<0.001).<br><br>Secondary:<br>Combination therapy significantly decreased FPG compared to placebo (treatment difference, -17.7 mg/dL; 95% CI, -24.3 to -11.0; P<0.001).<br><br>Combination therapy significantly decreased fasting serum proinsulin (P=0.009) and proinsulin:insulin ratio (P<0.001) compared to placebo.<br><br>Combination therapy significantly decreased TG compared to placebo (treatment difference, -11.2%; 95% CI, -22.0 to -0.4; P<0.041). There were no significant changes in other lipid parameters.<br><br>Combination therapy was well tolerated, with no increased risk of hypoglycemia compared to placebo. There was a significant increase in the incidence of abdominal pain with combination therapy compared to placebo. There was no difference in the change of body weight between the two treatments. |
| Bergenstal et al.[60] (2010) DURATION-2<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs | DB, DD, MC, PG, RCT<br><br>Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, $HbA_{1c}$ 7.1 to 11.0%, | N=514<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving an $HbA_{1c}$ ≤6.5 or ≤7.0%, FPG, six- | Primary:<br>Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased $HbA_{1c}$ compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165).<br><br>Secondary:<br>A significantly greater proportion of patients receiving exenatide achieved |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| sitagliptin 100 mg QD<br><br>vs<br><br>pioglitazone 45 mg QD<br><br>All patients received existing metformin therapy. | and BMI 25 to 45 kg/m$^2$ | | point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety | $HbA_{1c}$ targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone.<br><br>Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024).<br><br>In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported).<br><br>Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001).<br><br>Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).<br><br>Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001).<br><br>Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported).<br><br>All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406).<br><br>The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported. |
| Nauck et al.[61] (2007)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>glipizide 5 to 20 mg QD<br><br>All patients received metformin ≥1,500 | AC, DB, MC, NI, PG, RCT<br><br>Patients 18 to 78 years of age with type 2 diabetes who were inadequately controlled ($HbA_{1c}$ ≥6.5 and ≤10%) on metformin monotherapy | N=1,172<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, fasting insulin, proinsulin, and lipid parameters, β-cell function, insulin resistance and sensitivity, safety and tolerability, change in body | Primary:<br>In both treatments, the least squares mean $HbA_{1c}$ change from baseline was -0.67% (95% CI, -0.75 to -0.59).<br><br>A similar proportion of patients reached an $HbA_{1c}$ <7.0% in each group (63 vs 59%; difference of 3.9%; 95% CI, -2.8 to 10.7).<br><br>Secondary:<br>The change in FPG was not significantly different between the two treatments. The least squares change from baseline for sitagliptin was -0.56 mmol/L (95% CI, -0.81 to -0.30) and -0.42 mmol/L for glipizide (95% CI, -0.67 to -0.17). Sitagliptin led to a decrease in fasting proinsulin compared with an increase with glipizide. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| mg daily. | | | weight | Patients receiving glipizide demonstrated a higher rate of hypoglycemia as compared to patients receiving sitagliptin (32 vs 5%; P<0.001). No meaningful differences in overall serious clinical adverse events were observed between the two treatments.<br><br>Body weight significantly decreased with sitagliptin; the least squares mean change from baseline was -1.5 kg (95% CI, -2 to -0.9). Body weight significantly increased with glipizide with a least squares mean change from baseline of 1.1 kg (95% CI, 0.5 to 1.6). The between-treatment difference was -2.5 kg (95% CI, -3.1 to -2.0; P<0.001). |
| Hermansen et al.[62] (2007)<br><br>Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily<br><br>vs<br><br>sitagliptin 100 mg QD plus glimepiride 4 to 8 mg daily<br><br>vs<br><br>glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo<br><br>vs<br><br>glimepiride 4 to 8 | DB, DD, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 75 years of age, $HbA_{1c}$ 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin | N=441<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ (P<0.001) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in $HbA_{1c}$ compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32).<br><br>A significantly greater proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (17.1 vs 4.8%; P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an $HbA_{1c}$ <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638).<br><br>Secondary:<br>Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001).<br><br>Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported).<br><br>A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and QUICKI between the treatments. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| mg daily plus placebo | | | | Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 µIU/mL; P<0.001).<br><br>Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia.<br>A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1). |
| Arechavaleta et al.[63] (2011)<br><br>Sitagliptin 100 mg/day<br><br>vs<br><br>glimepiride 1 mg/day, titrated up to 6 mg/day | DB, NI, RCT<br><br>Patients with type 2 diabetes, $HbA_{1c}$ 6.5 to 9.0%, and on a stable dose of metformin (≥1,500 mg/day) combined with diet and exercise for ≥12 weeks | N=1,035<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary<br>Proportions of patients achieving $HbA_{1c}$ <7.0%, change in baseline FPG, hypoglycemia, body weight | Primary:<br>After 30 weeks, the least squares mean change in $HbA_{1c}$ from baseline was -0.47% with sitagliptin compared to -0.54% with glimepiride, with a between-group difference of 0.07% (95% CI, -0.03 to 0.16). This result met the prespecified criterion for declaring non-inferiority.<br><br>Secondary:<br>The proportions of patients with $HbA_{1c}$ <7.0% at week 30 were 52 and 60% with sitagliptin and glimepiride, respectively.<br><br>The least squares mean change in FPG from baseline was -0.8 mmol/L (95% CI, -1.0 to -0.6) with sitagliptin compared to -1.0 mmol/L (95% CI, -1.2 to -0.8) with glimepiride, for a between-group difference of 0.2 mmol/L (95% CI, -0.1 to 0.4).<br><br>The proportions of patients who reported hypoglycemia were 7 and 22% with sitagliptin and glimepiride (percentage-point difference, -15; P<0.001).<br><br>Relative to baseline, sitagliptin was associated with a mean weight loss compared to a mean weight gain with glimepiride (-0.8 vs 1.2 kg), yielding a between-group difference of -2.0 kg (*P*<0.001). |
| Srivastava et al.[64] (2012) | PG, RCT<br><br>Patients with type 2 | N=50<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>At 18 weeks, both treatments significantly (*P*<0.001) reduced baseline $HbA_{1c}$ (-0.636 vs -1.172%), with 12% of patients receiving sitagliptin and |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Sitagliptin 50 mg/day, titrated up to 100 mg/day<br><br>vs<br><br>glimepiride 1 mg/day, titrated up to 2 mg/day | diabetes inadequately controlled with metformin alone | | Secondary:<br>Change in baseline FPG and two-hour PPG, body weight, hypoglycemia | 36% of patients receiving glimepiride achieving target $HbA_{1c}$.<br><br>Secondary:<br>Reductions were significant (*P*<0.001) for both treatments in FPG (-15.49 vs -26.84 mg, respectively) and two-hour PPG (-34.28 vs -44.83 mg, respectively).<br><br>Sitagliptin showed a net decrease in body weight by 0.102 kg, whereas glimepiride showed net increase in body weight by 0.493 kg.<br><br>Incidence of hypoglycemia was 4 and 8% with sitagliptin and glimepiride. |
| Seck et al.[65] (2011)<br><br>Sitagliptin<br><br>vs<br><br>glimepiride | DB, RCT<br><br>Patients with type 2 diabetes receiving metformin | N=803<br><br>1 year | Primary:<br>Composite endpoint of $HbA_{1c}$ reduction, lack of hypoglycemia, and no body weight<br><br>Secondary:<br>Not reported | Primary:<br>Both treatments provided similar degrees of glycemic efficacy (least squares mean difference, -0.67%; between-group difference, -0.01; 95% CI, -0.09 to 0.08); however, significantly more patients receiving sitagliptin achieved an $HbA_{1c}$ reduction >0.5% without hypoglycemia and without an increase in body weight (least squares mean difference, -1.5 vs 1.1 kg; *P*<0.001; between-group difference, -2.5 kg; 95% CI, -3.1 to -2.0).<br><br>Patients receiving glipizide reported more than 10 times as many events of hypoglycemia compared to patients receiving sitagliptin.<br><br>Secondary:<br>Not reported |
| Perez-Monteverde et al.[66] (2011)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>sitagliptin/ metformin<br><br>vs | DB, RCT<br><br>Patients with type 2 diabetes and $HbA_{1c}$ 7.5 to 12.0% | N=492 (Phase 1)<br><br>12 weeks (Phase 1) plus 28 weeks (Phase 2) | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and 2-hour PPG, proportion of patients achieving $HbA_{1c}$ <7.0%, safety, body weight | Primary:<br>At the end of Phase 1 (12 weeks), mean changes from baseline in $HbA_{1c}$ were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase 2 (40 weeks), improvements in $HbA_{1c}$ were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; P=0.002).<br><br>Secondary:<br>At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for 2-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and 2-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| pioglitazone 30 to 45 mg QD<br><br>In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/ metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day | | | | Significantly more patients receiving combination therapy achieved an $HbA_{1c}$ <7.0% (55.0 vs 40.5%; P=0.004).<br><br>A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of oedema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was similarly low with both treatments.<br><br>Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001). |
| Wainstein et al.[67] (2012)<br><br>Sitagliptin/ metformin 50/500 mg BID, titrated up to 50/1,000 mg BID<br><br>vs<br><br>pioglitazone 30 mg/day, titrated up to 45 mg/day | DB, RCT<br><br>Treatment-naïve patients with type 2 diabetes $HbA_{1c}$ 7.5 to 12.0% | N=517<br><br>32 weeks | Primary:<br>Change from baseline $HbA_{1c}$, proportion of patients who achieved $HbA_{1c}$ <7.0%<br><br>Secondary:<br>Change from baseline FPG | Primary:<br>The least squares mean changes in $HbA_{1c}$ at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001).<br><br>A greater proportion of patients achieved an $HbA_{1c}$ <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001).<br><br>Secondary:<br>Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy.<br><br>Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001).<br><br>Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of oedema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone.<br><br>There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055). |
| Scott et al.[68] (2008)<br><br>Sitagliptin 100 mg QD plus metformin (existing therapy)<br><br>vs<br><br>rosiglitazone 8 mg QD plus metformin (existing therapy)<br><br>vs<br><br>metformin (existing therapy) plus placebo | AC, DB, MC, PG, RCT<br><br>Type 2 diabetics 18 to 75 years of age receiving stable metformin doses (≥1,500 mg/day for ≥10 weeks) and inadequate glycemic control ($HbA_{1c}$ ≥7.0 and ≤11.0%) | N=273<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; P≤0.001). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14).<br><br>The proportion of patients achieving an $HbA_{1c}$<7.0% was significantly greater with sitagliptin (55%; P=0.006) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported).<br><br>Secondary:<br>Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; P≤0.001) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported).<br><br>Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; P≤0.05) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported).<br><br>Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).<br><br>Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 µIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 µIU/mL; 95% CI, -5.50 to -1.40; P value not reported).<br><br>The proinsulin:insulin ratio was similar across all treatments.<br><br>Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; P≤0.05) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; P≤0.05) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Derosa et al.[69] (2010)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>metformin 850 mg BID<br><br>All patients were receiving pioglitazone (15 or 30 mg/day). | DB, RCT<br><br>Patients with type 2 diabetes, $HbA_{1c}$ >7.5%, and receiving pioglitazone 30 mg/day | N=151<br><br>12 months | Primary:<br>Body weight, BMI, $HbA_{1c}$, FPG, PPG, fasting plasma insulin, HOMA-IR, HOMA-B, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, adiponectin, resistin, TNF-α, high sensitivity CRP<br><br>Secondary:<br>Not reported | Primary:<br>A decrease in body weight and BMI were observed in patients receiving metformin, which was not observed in patients receiving sitagliptin.<br><br>Significant decreases in $HbA_{1c}$, FPG, and PPG, and significant increases in HOMA-B were comparable between the two treatment groups.<br><br>Fasting plasma insulin, fasting plasma proinsulin, proinsulin/fasting plasma insulin ratio, and HOMA-IR were decreased with both treatments. While values were lower with metformin, there were no significant differences observed between the two treatments.<br><br>Sitagliptin achieved no significant changes in changes in adiponectin, resistin, TNF-α, compared to a significant increase in adiponectin and significant decreases in resistin and TNF-α achieved with metformin.<br><br>High sensitivity CRP decreased significantly with both treatments, with no difference between them.<br><br>Secondary:<br>Not reported |
| Rigby et al.[70] (2010)<br><br>Sitagliptin 100 mg QD and metformin (existing therapy)<br><br>vs<br><br>rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy)<br><br>vs | OL<br><br>Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control ($HbA_{1c}$ 6.5 to 10.0% on a stable regimen of metformin (1,500 to 2,550 mg daily), with LDL-C ≥60 mg/dL and TG <500 mg/dL | N=169<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to week 16<br><br>Secondary:<br>Change in $HbA_{1c}$ from baseline to week eight, change in FPG and fasting insulin from baseline to weeks eight and 16, change in two-hour PPG and postprandial | Primary:<br>At week 16, $HbA_{1c}$ was reduced from baseline in all treatment groups (least square mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009).<br><br>Secondary:<br>At week eight, $HbA_{1c}$ was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109).<br><br>FPG was significantly reduced from baseline at week eight and week 16 in all treatment groups.<br><br>The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy) | | | insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an $HbA_{1c}$ reduction >0.7% from baseline, percentage of participants who achieved $HbA_{1c}$ <7.0% | There was no significant change in fasting insulin or two-hour postprandial insulin from baseline to week 16 in any treatment group.<br><br>Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008).<br><br>LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011).<br><br>TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median triglyceride levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment.<br><br>At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in $HbA_{1c}$ 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved $HbA_{1c}$ <7.0%.<br><br>The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity. |
| Vilsbøll et al.[71] (2010)<br><br>Sitagliptin 100 mg QD | RCT, DB, PC, PG<br><br>Patients ≥21 years of age with type 2 diabetes on insulin | N=641<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary: | Primary:<br>At week 24, the addition of sitagliptin to insulin therapy (± metformin) significantly reduced $HbA_{1c}$ by 0.6% (P<0.001) compared with no change in the placebo group. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>placebo<br><br>All patients received insulin therapy with or without metformin. | (≥15 IU/day) alone or in combination with metformin (≥1500 mg/day) who had inadequate glycemic control ($HbA_{1c}$ 7.5 to 11%), and BMI 20 to 43 $kg/m^2$ | | FPG, two-hour postmeal glucose, and the proportion of patients with an $HbA_{1c}$ <7.0% or <6.5% at week 24 | Secondary:<br>At week 24, mean change in FPG from baseline was -18.5 mg/dL in the sitagliptin group compared to -3.5 mg/dL in the placebo group (P<0.001).<br><br>The two-hour post meal glucose was significantly reduced from baseline in the sitagliptin group (−30.9 mg/dL) compared to placebo (+5.2 mg/dL; P<0.001).<br><br>The proportion of patients with an $HbA_{1c}$ <7.0% at week 24 was significantly higher in the sitagliptin group compared with the placebo group (13 vs 5%, respectively). There was no difference between groups in the proportion of patients with an $HbA_{1c}$ <6.5% at week 24. |
| Esposito et al.[72] (2011)<br><br>Alogliptin* 12.5 to 25 mg QD<br><br>vs<br><br>saxagliptin 5 mg QD<br><br>vs<br><br>sitagliptin 100 mg QD<br><br>vs<br><br>vildagliptin* 100 mg QD | MA (43 RCT)<br><br>Type 2 diabetics were treatment-naïve or receiving background therapy with other agents | N=19,101<br><br>Duration not reported | Primary:<br>Proportion of patients achieving an $HbA_{1c}$ <7.0%, change in baseline body weight, incidence of hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>Proportion of patients achieving an $aHbA_{1c}$ <7.0%<br>Treatment with saxagliptin demonstrated a greater chance to achieve n $HbA_{1c}$ <7.0% compared to placebo (POR, 2.81; 95% CI, 2.31 to 3.72), but not compared to comparator drugs (POR, 0.95; 95% CI, 0.8 to 1.11). Saxagliptin was associated with a greater decrease in $HbA_{1c}$ compared to placebo (WMD, -0.69%; 95% CI, -0.1 to -0.37), but not compared to comparator drugs (WMD, 0.15%; 95% CI, -0.14 to 1.7).<br><br>Sitagliptin was associated with a greater chance to achieve an $HbA_{1c}$ <7.0% compared to placebo (POR, 3.15; 95% CI, 2.47 to 3.72), but not compared to comparator drugs (POR, 0.70; 95%CI, 0.35 to 1.12). Sitagliptin was also associated with a greater decrease in $HbA_{1c}$ compared to placebo (WMD, -0.78%; 95% CI, -0.93 to -0.63), but not compared to comparator drugs (WMD, 0.19%; 95% CI, -0.13 to 0.52).<br><br>Change in baseline body weight<br>Saxagliptin was associated with small and no significant changes in body weight compared to baseline or other comparator drugs (WMD, -0.56 kg; 95% CI, -2.8 to 1.7), but with a significant difference compared to placebo (0.63 kg; 95% CI, 0.03 to 1.17).<br><br>The absolute change in weight was small and not significantly different from baseline with sitagliptin (0.08 kg); however, the difference compared to placebo was significant (WMD, 0.48 kg; 95% CI, 0.19 to 0.77). The |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | overall change in weight with sitagliptin was not different from that of comparator drugs.<br><br>Incidence of hypoglycemia<br>Saxagliptin was associated with similar risk of hypoglycemia compared to placebo (RR, 1.1; 95% CI, 0.81 to 1.42) and comparator drugs (RR, 0.55; 95% CI, 0.4 to 1.9).<br><br>Sitagliptin was associated with a significantly lower risk of hypoglycemia compared to placebo (RR, 1.8; 95% CI, 0.61 to 2.5) and comparator drugs (RR, 0.87; 95% CI, 0.30 to 2.80).<br><br>Secondary:<br>Not reported |

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, ES=extension study, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, SA=single-arm, SR=systematic review, XO=cross-over
Miscellaneous: AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, $HbA_{1c}$=glycosylated hemoglobin, HDL-C=high density lipoprotein-cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein-cholesterol, MI=myocardial infarction, OR=odds ratio, PGWB=Psychological General Well-being index, PPG=post-prandial glucose, POR=pooled odds ratio, QOL=quality of life, QUICKI=Quantitative insulin sensitivity check index, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TNF-α=tumor necrosis factor-α, TZD=thiazolidinedione, WMD=weighted mean difference

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 10. Relative Cost of the Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| **Single Entity Agents** | | | | |
| Linagliptin | tablet | Tradjenta® | $$$$$ | N/A |
| Saxagliptin | tablet | Onglyza® | $$$$$ | N/A |
| Sitagliptin | tablet | Januvia® | $$$$$ | N/A |
| **Combination Products** | | | | |
| Linagliptin and metformin | tablet | Jentadueto® | $$$$$ | N/A |
| Saxagliptin and metformin | extended-release tablet | Kombiglyze XR® | $$$$$ | N/A |
| Sitagliptin and metformin | extended-release, tablet, tablet | Janumet®, Janumet XR® | $$$$$ | N/A |
| Sitagliptin and simvastatin | tablet | Juvisync® | $$$$$ | N/A |

N/A=Not available

## X. Conclusions

The dipeptidyl peptidase-4 (DPP-4) inhibitors are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Available DPP-4 inhibitor combination products, with metformin and simvastatin, are available for use when treatment with both drug components is appropriate.[1-8]

There are no generic products available; however, metformin and simvastatin are available generically in a separate formulation.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin ($HbA_{1c}$) will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The DPP-4 inhibitors are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia and an established efficacy and safety profile when used in combination with metformin as advantages associated with the DPP-4 inhibitors compared to other classes of antidiabetic agents. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DDP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one DPP-4 inhibitor over another is not stated.[9-18]

A variety of clinical trials have been conducted with the DPP-4 inhibitors. The majority of the clinical trials have compared active treatment to placebo in patients not adequately controlled on other antidiabetic medications. In these trials, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[21-72] In treatment naïve patients, sitagliptin was shown to be non-inferior to metformin when used as monotherapy; however, monotherapy with exenatide was more beneficial with regards to glycemic parameters compared to monotherapy with sitagliptin.[30,31] Sitagliptin was also shown to be as effective as rosiglitazone or glipizide when these agents were added to existing metformin monotherapy.[61,68] The addition of exenatide to metformin led to a greater reduction in two-hour postprandial glucose concentrations compared to the addition of sitagliptin to metformin.[29] Limited head-to-head clinical trials comparing DDP-4 inhibitors have been conducted. In one trial saxagliptin demonstrated non-inferiority to sitagliptin when both agents were added to existing metformin therapy.[51] There have been minimal clinical efficacy or safety trials conducted with any of the DPP-4 inhibitor fixed-dose combination products; bioequivalence of these products with co-administration of the individual drug components has been demonstrated for all tablet strengths.[4-8] Available trials evaluating the fixed-dose combination of sitagliptin and metformin support its efficacy and safety in the management of type 2 diabetes. Specifically, combination therapy was associated with significantly improved glycemic control compared to metformin monotherapy.[58]

The DPP-4 inhibitors are generally well tolerated. There have been postmarketing reports of serious hypersensitivity reactions in patients taking a DDP-4 inhibitor. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. There have also been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking a DPP-4 inhibitor. Combination DPP-4 inhibitor products containing metformin are associated with a risk of lactic acidosis.[1-8]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the DPP-4 inhibitors or any other antidiabetic drug.[1-8]

There is insufficient evidence to support that one brand DPP-4 inhibitor is safer or more efficacious than another within its given indication. Since the DPP-4 inhibitors are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, they should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand DPP-4 inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

## XII. References

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Incretin Mimetics
# AHFS Class 682006
# November 14, 2012

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The incretin mimetics are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-3] The incretin mimetics are glucagon-like peptide-1 (GLP-1) receptor agonists. GLP-1 is a human incretin hormone that is secreted from the small intestine in response to food intake, which has multiple effects on the stomach, liver, pancreas and brain to control glucose concentrations. Human GLP-1 is inactivated by the dipeptidyl peptidase-4 (DPP4) enzyme within minutes. Endogenous GLP-1 levels have been shown to be reduced in patients with type 2 diabetes. Exenatide is a synthetic peptide with approximately 50% homology to human GLP-1, but is more resistant to inactivation by DPP-4. It enhances glucose-dependent insulin secretion by pancreatic beta cells, suppresses glucagon secretion, slows gastric emptying and reduces food intake.[1-5]

The incretin mimetics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. This class was last reviewed in May 2010.

**Table 1. Incretin Mimetics Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Exenatide | injection | Byetta®, Bydureon® | none |
| Liraglutide | injection | Victoza® | none |

PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Incretin Mimetics**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[6] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes<br>• An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[7] (2012)** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy.<br><br>Initial drug therapy<br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br><u>Advancing to dual combination therapy</u><br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.<br>• Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.<br>• It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.<br>• For all medications, consideration should also be given to overall tolerability.<br><br><u>Advancing to triple combination therapy</u><br>• Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.<br>• Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.<br>• In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.<br>• Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient |

<table>
<tr><th>Clinical Guideline</th><th>Recommendation(s)</th></tr>
<tr><td></td><td>adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations

<table>
<tr><td>Initial Drug Monotherapy</td><td colspan="5">Metformin</td></tr>
<tr><td>Efficacy (↓$HbA_{1c}$)</td><td colspan="5">High</td></tr>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonyl-urea</td><td>Metformin + thia-zolidinedione (TZD)</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor agonist</td><td>Metformin + insulin (usually basal)</td></tr>
<tr><td>Efficacy (↓$HbA_{1c}$)</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypo-glycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Oedema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td rowspan="2">Three Drug Combin-ations</td><td>Metformin + sulfonyl-urea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td>TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table>
</td></tr>
<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[8] (2012)</td><td>• Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.<br>• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.<br>• It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[9] (2011)</td><td><u>Antihyperglycemic pharmacotherapy</u><br>• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[10]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.</td></tr>
</table>

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus:<br>**Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus:**<br>**An Algorithm for Glycemic Control[10] (2009)** | Principles underlying the algorithm<br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action.<br>• Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br>Stratification by current $HbA_{1c}$<br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br><u>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%</u><br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated.<br>• The following triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + GLP-1 receptor agonist + glinide.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>  ○ Metformin + DPP-4 inhibitor + glinide. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>○ Metformin + GLP-1 receptor agonist.<br>○ Metformin + DPP-4 inhibitor.<br>○ Metformin + TZD.<br>○ Metformin + sulfonylurea.<br>○ Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>○ Metformin + GLP-1 receptor agonist + TZD.<br>○ Metformin + DPP-4 inhibitor + TZD.<br>○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>○ Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>  ○ Metformin + TZD.<br>  ○ Metformin + TZD + sulfonylurea.<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[11] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>  ○ Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>  ○ Initiate self-monitoring blood glucose levels.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>• First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>• After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>• Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>• Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>• Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[12] (2009)** | <u>DPP-4 inhibitors</u><br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br><u>TZDs</u><br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  o A body mass index ≥35 $kg/m^2$ in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI <35 $kg/m^2$, and thera$^{p}$y with insulin would have significant occupational implications or weight loss would benefit other sig$^{n}$ificant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u> |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  o A person prefers injecting insulin immediately before a meal<br>  o Hypoglycemia is a problem.<br>  o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>  o Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>  o Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>  o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>  o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>• Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[13] (2008)** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br><u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>  o The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>  o A sulfonylurea if metformin is not tolerated.<br>  o Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br><u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u><br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/m$^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  o Inadequate blood glucose control ($HbA_{1c}$ ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  o Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  o Continue with metformin and the sulfonylurea (and acarbose, if used)<br>  o Review the use of the sulfonylurea if hypoglycemia occurs<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>  o Continue with metformin<br>  o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Consider combining pioglitazone with insulin therapy for:<br>  ○ Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>  ○ Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>  ○ Those who require assistance from a care taker or healthcare professional to administer their insulin injections<br>  ○ Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes<br>  ○ Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ is >9.0%. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>  ○ Immediate injection before a meal is preferred.<br>  ○ Hypoglycemia is a problem.<br>  ○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI):<br>**Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[14] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |
| International Diabetes Federation (IDF) Clinical Guidelines Task Force:<br>**Global Guideline for Type 2 Diabetes[15] (2005)** | <u>Lifestyle management</u><br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br><u>Oral therapy</u><br>• Metformin should be considered first-line therapy, unless contraindicated. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br><u>Insulin</u><br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the incretin mimetics are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

It is important to note that the incretin mimetics are not a substitute for insulin, and these agents should not be used in type 1 diabetics or for the treatment of diabetic ketoacidosis. The incretin mimetics would not be effective in these situations.[1-3]

According to FDA-approved package labeling, due to the uncertain relevance of the rat thyroid C-cell tumor findings to humans, exenatide (Bydureon®) and liraglutide are not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.[2,3]

**Table 3. FDA-Approved Indications for the Incretin Mimetics[1-3]**

| Generic Name | Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus |
|---|---|
| Exenatide | ✔ |
| Liraglutide | ✔ |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the incretin mimetics are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the Incretin Mimetics[4]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| Exenatide | 65 to 76† | Not reported | Plasma/tissues (% not reported) | Renal (% not reported) | 2.4 |
| Liraglutide | 55 | >98 | Not significant (% not reported) | Renal (0 unchanged; 6 | 13 |

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| | | | | changed), Feces (0 unchanged; 5 unchanged) | |

†Information derived from animal data.

## V. Drug Interactions

There are no significant drug interactions reported with the incretin mimetics.[5] However, exenatide slows gastric emptying which can reduce the extent and rate of absorption of orally administered drugs. Exenatide should be used with caution in patients receiving oral medications that have a narrow therapeutic index or require rapid gastrointestinal absorption. Patients should be advised to take oral medications that are dependent on threshold concentrations for efficacy (e.g., contraceptives and antibiotics) at least one hour before exenatide.[1,2]

## VI. Adverse Drug Events

The most common adverse drug events reported with the incretin mimetics are listed in Table 5. The boxed warning for the incretin mimetics are listed in Tables 6 and 7. Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Patients may develop antibodies to exenatide consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small percentage of patients, the formation of antibodies to exenatide at high titers could result in failure to achieve adequate improvement in glycemic control.[1,2]

**Table 5. Adverse Drug Events (%) Reported with the Incretin Mimetics[1-3]**

| Adverse Event | Exenatide/Exenatide Extended-Release | Liraglutide |
|---|---|---|
| Anorexia | - | 9 |
| Asthenia | 4 | - |
| Back pain | - | 5 |
| Constipation | -/6.3 to 10.1 | 5.1 to 9.9 |
| Decreased appetite | 1 to 2/5 | 9.3 |
| Diarrhea | 1 to 13/9.3 to 20.0 | 7.2 to 17.1 |
| Dizziness | 1 to 9 | 5.2 |
| Dyspepsia | 3 to 7/5.0 to 7.4 | 5.2 to 6.5 |
| Fatigue | -/5.6 to 6.1 | 5.1 |
| Feeling jittery | 9 | - |
| Gastroenteritis viral | -/8.8 | - |
| Gastroesophageal reflux disease | 3/7.4 | - |
| Headache | 9/6.1 to 9.9 | 8.2 to 9.6 |
| Hyperhidrosis | 3 | - |
| Hypertension | - | 3 |
| Hypoglycemia | 3.8 to 35.7/0 to 20 | 0.1 to 27.4 |
| Influenza | - | 7.4 |
| Injection site erythema | -/5.4 to 7.4 | - |
| Injection site hematoma | -/5.4 | - |
| Injection site nodule | -/6.0 to 10.5 | - |
| Injection site pruritis | -/5.0 to 18.2 | - |
| Nasopharyngitis | - | 5.2 |
| Nausea | 8 to 44/11.3 to 27.0 | 7.5 to 34.6 |
| Sinusitis | - | 5.6 |
| Upper respiratory tract infection | - | 9.5 |
| Urinary tract infection | - | 6 |

| Adverse Event | Exenatide/Exenatide Extended-Release | Liraglutide |
|---|---|---|
| Vomiting | 4 to 13/10.8 to 11.3 | 6.5 to 12.4 |

*Corresponds to monotherapy or combination therapy with other antidiabetic therapies.
-Event not reported.

**Table 6. Boxed Warning for Bydureon® (exenatide extended-release)[2]**

| WARNING |
|---|
| Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether exenatide extended-release causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be determined by clinical or nonclinical studies. Exenatide extended-release is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2. Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with exenatide extended-release. Patients should be counseled regarding the risk and symptoms of thyroid tumors. |

**Table 7. Boxed Warning for Victoza® (liraglutide)[3]**

| WARNING |
|---|
| Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors. |

## VII. Dosing and Administration

The usual dosing regimens for the incretin mimetics are listed in Table 8. The incretin mimetics are administered by subcutaneous injection. There are currently two formulations of exenatide available. The immediate-release formulation (Byetta®) is administered twice daily and should be given within 60 minutes prior to a meal, while the extended-release (ER) formulation (Bydureon®) is administered once weekly and can be administered without regard to meals.[1,2] The extended effect of exenatide ER results from the addition of a biodegradable polymer poly D, L-lactic-co-glycolic acid to the active component, exenatide, which forms microspheres. After exenatide ER is administered, continued infiltration of water into the microspheres causes them to swell and release the medication in a slow predictable fashion. Of note, patients who administer exenatide ER will have a palpable SC nodule at the injection site that dissipates as the medication is released.[16] Liraglutide is administered once daily and can also be administered without regard to meals.[3]

**Table 8. Usual Dosing Regimens for the Incretin Mimetics[1-3]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| Exenatide | <u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u><br>Injection (Bydureon®): initial, 2 mg SC once weekly<br><br>Injection (Byetta®): initial, 5 µg SC BID; maintenance, 10 µg SC BID after one month of therapy | Safety and efficacy have not been established in pediatric patients. | Injection:<br>5 µg/0.02 mL (Byetta®)*<br>10 µg /0.04 mL (Byetta®)†<br>2 mg/vial (Bydureon)‡ |
| Liraglutide | <u>Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:</u><br>Injection: initial, 0.6 mg SC QD for one | Safety and efficacy have not been established in pediatric patients. | Injection:<br>6 mg/mL§ |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | week; maintenance, 1.2 to 1.8 mg SC QD | | |

BID=twice daily, QD=once daily, SC=subcutaneous
*Supplied as a pre-filled syringe (1.2 mL, 60 doses).
†Supplied as a pre-filled syringe (2.4 mL, 60 doses).
‡Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide, one pre-filled syringe, one vial connector, and two custom needles).
§Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the incretin mimetics are summarized in Table 9.

**Table 9. Comparative Clinical Trials with the Incretin Mimetics**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Type 2 Diabetes – Monotherapy** | | | | |
| Moretto et al.[17] (2008)<br><br>Exenatide 5 µg BID<br><br>vs<br><br>exenatide 10 µg BID<br><br>vs<br><br>placebo | DB, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes who were drug naïve and whose diabetes was inadequately controlled on diet and exercise alone | N=232<br><br>24 weeks | Primary:<br>$HbA_{1c}$, fasting serum glucose, six-point self-monitored blood glucose, proportions of patients achieving $HbA_{1c}$ values ≤6.5 and ≤7.0%, weight; HOMA-B, safety<br><br>Secondary:<br>Not reported | Primary:<br>Mean changes in $HbA_{1c}$ from baseline (LSM) were significantly greater with exenatide 5 and 10 µg compared to placebo (-0.7 and -0.9 vs -0.2%, respectively; P=0.003 and P<0.001 vs placebo).<br><br>Mean changes in fasting serum glucose from baseline were significantly greater with exenatide 5 and 10 µg compared to placebo (-17.5 and -18.7 vs -5.2 mg/dL, respectively; P=0.029 and P=0.016 vs placebo).<br><br>Changes in daily mean PPG excursions from baseline to end point were significantly greater with exenatide 5 and 10 µg compared to placebo (-21.3 and -24.7 vs -8.3 mg/dL, respectively; P<0.001 vs placebo for both).<br><br>With exenatide 5 and 10 µg, 31 and 35% of patients achieved $HbA_{1c}$ ≤6.5% at end point vs 19% of patients receiving placebo (P value not significant and P=0.026, respectively), while 48 and 46 vs 29% of patients achieved $HbA_{1c}$ ≤7.0% (P=0.024 and P=0.036, respectively).<br><br>Changes in weight at 24 weeks were greater with exenatide 5 and 10 µg compared to placebo (-2.8 and -3.1 vs -1.4 kg, respectively; P=0.004 and P<0.001).<br><br>HOMA-B values increased from baseline to end point by 32 and 28% with exenatide 5 and 10 µg, respectively, compared to 6% with placebo. Improvements from baseline to end point in HOMA-B were significantly greater with exenatide 5 and 10 µg compared to placebo (P=0.002 and P=0.010, respectively).<br><br>Significant improvements in mean SBP and DBP from baseline to end point were also observed with exenatide (SBP: exenatide 5 and 10 µg, -3.7 mm Hg; P=0.037, DBP: exenatide 10 µg, -2.3 mm Hg; P=0.046) compared to placebo (SBP: -0.3 mm Hg and DBP: -0.3 mm Hg). |

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| | | | | Overall, 25% of patients reported at least one treatment-emergent adverse event. Nausea was reported with the greatest incidence (exenatide 5 µg, 3%; exenatide 10 µg, 13%; placebo, 0%; P=0.010 for the combined exenatide group vs placebo). Most (88%) treatment-emergent adverse events were mild or moderate in intensity.<br><br>Hypoglycemia was reported in five, four, and one percent of patients receiving exenatide 5 and 10 µg and placebo groups, respectively (P value not significant), with no incidents of severe hypoglycemia reported. |
| DeFronzo et al.[18] (2008)<br><br>Exenatide 5 µg BID for 1 week, then 10 µg BID for 1 week<br><br>vs<br><br>sitagliptin 100 mg QD for 2 weeks<br><br>All patients were receiving existing metformin regimens. | DB, MC, RCT, XO<br><br>Patients 18 to 70 years of age with type 2 diabetes who were treated with a stable regimen of metformin, $HbA_{1c}$ 7.0 to 11.0%, FPG <280 mg/dL, and BMI 25 to 45 kg/m$^2$ | N=95<br><br>4 weeks | Primary:<br>2-hour PPG<br><br>Secondary:<br>Postprandial insulin, glucagon, active GLP-1 and TG concentrations, and safety | Primary:<br>The 2-hour PPG concentration (LSM) was lower for exenatide compared to sitagliptin (133 vs 208 mg/dL; P<0.0001). In the ITT population, the 2-hour PPG concentration was lower with exenatide compared to sitagliptin (166 vs 210 mg/dL, respectively; P<0.0001).<br><br>The change in 2-hour PPG concentration (least square mean) from baseline was -112 mg/dL for exenatide compared to -37 mg/dL for sitagliptin (P<0.0001).<br><br>FPG was similar following treatment with exenatide (-15 mg/dL) and sitagliptin (-19 mg/dL; P=0.3234).<br><br>Following crossover to the alternate therapy, patients switched from exenatide to sitagliptin experienced an increase in mean 2-hour PPG +73 mg/dL. Patients switched from sitagliptin to exenatide treatment experienced a reduction in the mean 2-hour PPG concentration -76 mg/dL.<br><br>Secondary:<br>The acute insulin response was greater for exenatide compared to sitagliptin (P=0.0017).<br><br>Both exenatide and sitagliptin reduced the mean postprandial plasma glucagon concentration compared to baseline; however, the reduction was greater with exenatide compared to sitagliptin (P=0.0011).<br><br>Both exenatide and sitagliptin both reduced mean postprandial TG concentrations compared to baseline; however, the decrease was greater with |

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| | | | | exenatide compared to sitagliptin (P=0.0118).<br><br>Exenatide reduced the rate of gastric emptying compared to baseline and to sitagliptin (P<0.0001). Sitagliptin had no effect on gastric emptying).<br><br>Adverse events with exenatide and sitagliptin were mild-to-moderate. The most common adverse events were gastrointestinal with both treatments. Nausea was experienced by 34% of patients treated with exenatide and 12% of patients treated with sitagliptin. Vomiting was experienced by 24% of patients treated with exenatide and 3% of patients treated with sitagliptin. No serious treatment-emergent adverse events were reported during the study. |
| Bergenstal et al.[19] (2009)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID<br><br>vs<br><br>insulin aspart 12 units QD before dinner (BIAsp 30 QD)<br><br>vs<br><br>insulin aspart 12 units divided equally before breakfast and dinner (BIAsp 30 BID)<br><br>All patients were receiving metformin with or without a | OL, PG, RCT<br><br>Patients 18 to 80 years of age with type 2 diabetes mellitus and $HbA_{1c}$ ≥8%, insulin-naïve, and receiving treatment with metformin and a sulfonylurea for at least 3 months prior to enrolling in the study | N=372<br><br>24 Weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>FPG, eight-point plasma glucose profiles, changes in body weight | Primary:<br>At 24 weeks, $HbA_{1c}$ values were 7.61, 7.75, 8.46% for BIAsp 30 BID, BIAsp 30 QD, and exenatide, respectively (both P<0.0001 compared to exenatide).<br><br>At the end of the study, 37% of patients in the BIAsp 30 BID group achieved an $HbA_{1c}$ <7.0% compared to 20% of patients in the exenatide group (P=0.0060). Additionally, 25% of patients in the BIAsp 30 BID group achieved an $HbA_{1c}$ ≤6.5% compared with 8% in the exenatide group (P=0.0004).<br><br>At the end of the study, 26% of patients in the BIAsp 30 QD group achieved an $HbA_{1c}$ <7.0% compared to 20% of patients in the exenatide group (P=0.3488). Additionally, 12% of patients in the BIAsp 30 QD group achieved an $HbA_{1c}$ ≤6.5% compared with 8% in the exenatide group (P=0.3802).<br><br>The percentage of patients who achieved $HbA_{1c}$ ≤6.5% was higher with BIAsp 30 BID compared to BIAsp 30 QD (25 vs 12%; P=0.0122).<br><br>Secondary:<br>There were significant changes in FPG with BIAsp 30 BID (-62.7 mg/dL; P<0.0001 vs exenatide) and BIAsp 30 QD (-52.4 mg/dl; P=0.0002 vs exenatide) compared to exenatide (-21.4 mg/dL).<br><br>At the end of the study, the eight-point plasma glucose profiles were significantly lower with BIAsp 30 BID and BIAsp 30 QD than exenatide. |

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| sulfonylurea.<br><br>Insulin dose was titrated as necessary. | | | | At 24 weeks, hypoglycemia was reported in 56% of patients in the BIAsp 30 QD group, 61% of patients in the BIAsp 30 BID group, and 29% in the exenatide group.<br><br>Weight loss was reported in the exenatide group (-1.9 kg) compared with weight gain in the BIAsp 30 QD (+2.8 kg) and BIAsp 30 BID (4.1 kg).<br><br>There were more reports of nausea and vomiting with exenatide than in the insulin groups. |
| Russell-Jones et al.[20] (2012) DURATION-4<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>metformin 2,000 mg/day<br><br>vs<br><br>pioglitazone 45 mg/day<br><br>vs<br><br>sitagliptin 100 mg/day | DB, DD, MC, PG, RCT<br><br>Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with $HbA_{1c}$ 7.1 to 11.0%, BMI 23 to 45 kg/m$^2$, and stable weight | N=820<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported QOL | Primary:<br>Decreases in $HbA_{1c}$ were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The $HbA_{1c}$ at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively.<br><br>Secondary:<br>Similar proportions of patients receiving exenatide ER and metformin achieved $HbA_{1c}$ <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved $HbA_{1c}$ <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001).<br><br>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26).<br><br>Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.<br><br>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was |

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| | | | | sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892).<br><br>No clinically significant changes in serum lipids were observed with any treatment.<br><br>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329).<br><br>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.<br><br>All treatments resulted in improvements in perceived treatment satisfaction, weight-related QOL, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related QOL, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (P values not reported). |
| Fakhoury et al.[21] (2010)<br><br>Incretin-based | MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, | N=Not reported<br><br>Duration | Primary:<br>Change in baseline $HbA_{1c}$ and weight, hypoglycemia | Primary:<br>Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease $HbA_{1c}$ compared to placebo. |

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| therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin)<br><br>vs<br><br>placebo | vildagliptin)<br><br>Type 2 diabetics ≥18 years of age | varied (4 to 52 weeks | Secondary: Not reported | Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline $HbA_{1c}$. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant.<br><br>There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; P<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; P=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide.<br><br>Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; P=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; P=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; P=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; P=0.050).<br><br>Secondary: Not reported |
| Monami et al.[22] (2011)<br><br>GLP-1 receptor agonist based therapies (albiglutide*, exenatide, liraglutide, lixisenatide*, semaglutide*, and | MA<br><br>Type 2 diabetics | N=10,485<br><br>Up to 52 weeks | Primary: Major cardiovascular events<br><br>Secondary: Not reported | Primary: GLP-1 receptor agonists are not associated with an increased risk of cardiovascular events (OR, 0.74; 95% CI, 0.50 to 1.08; P=0.12).<br><br>Exenatide is not associated with an increased risk of cardiovascular events (OR, 0.85; 95% CI, 0.50 to 1.45; P=0.55).<br><br>Liraglutide is not associated with an increased risk of cardiovascular events (OR, 0.69; 95% CI, 0.40 to 1.22; P=0.20).<br><br>In PC trials, GLP-1 receptor agonists reduced the risk of cardiovascular |

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| taspoglutide*)<br><br>vs<br><br>other classes of antidiabetic medications or placebo | | | | events (OR, 0.46; 95% CI, 0.25 to 0.83; P=0.009).<br><br>In AC trials, there was no difference between treatments in the risk of cardiovascular events (OR, 1.05; 95% CI 0.63 to 1.76; P=0.84).<br><br>Secondary:<br>Not reported |
| Shyangdan et al.[23] (2011)<br><br>GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)<br><br>vs<br><br>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas) | MA (RCTs)<br><br>Type 2 diabetics ≥18 years of age | N=not reported<br><br>8 to 26 weeks | Primary:<br>Change in baseline $HbA_{1c}$, incidence of hypoglycemia, weight change<br><br>Secondary:<br>Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function | Primary:<br>Change in baseline $HbA_{1c}$<br>Exenatide ER significantly decreased $HbA_{1c}$ compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an $HbA_{1c}$ <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an $HbA_{1c}$ <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).<br><br>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased $HbA_{1c}$ (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in $HbA_{1c}$ compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).<br><br>Compared to placebo, liraglutide 1.8 mg significantly decreased an $HbA_{1c}$ (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg |

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| | | | | were more likely to achieve $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in $HbA_{1c}$ compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).<br><br>Liraglutide decreased $HbA_{1c}$ to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).<br><br>Liraglutide 1.2 mg was associated with a non-significant increase in $HbA_{1c}$ compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an $HbA_{1c}$ <7.0% compared to the 1.8 mg dose (P=0.92).<br><br>Incidence of hypoglycemia<br>The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).<br><br>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs |

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| | | | | (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).<br><br>Weight loss<br>Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).<br><br>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).<br><br>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).<br><br>Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).<br><br>Secondary:<br>Data on mortality and morbidity were not reported for any treatment.<br><br>QOL<br>Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; |

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| | | | | P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.<br><br>Data for liraglutide were not reported.<br><br>Safety<br>Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).<br><br>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.<br><br>BP<br>There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. |

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| | | | | FPG<br>There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).<br><br>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).<br><br>PPG<br>There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).<br><br>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable.<br><br>Lipid profile<br>TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | β cell function<br>Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio. |
| Pinelli et al.[24] (2011)<br><br>GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*)<br><br>vs<br><br>exenatide and sitagliptin | MA, SR (5 RCTs)<br><br>Adult type 2 diabetics | N=not reported<br><br>Duration varied (not reported) | Primary:<br>Change in baseline $HbA_{1c}$, FPG, PPG, weight , BP, and lipid profile; safety<br><br>Secondary:<br>Not reported | Primary:<br>Pooled analysis demonstrates modest decreases in $HbA_{1c}$ favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve $HbA_{1c}$ <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31).<br><br>Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04).<br><br>In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; P=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast (treatment difference, -24 mg/dL; P<0.0001) and dinner (-18 mg/dL; P=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (P<0.05).<br><br>Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44).<br><br>In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; P=0.006), but results were not significant in the three other trials (P values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; P=0.02). Between-group differences were not significant in the other three trials (P values not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; P value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; P=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; P=0.05).<br><br>No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritis in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment.<br><br>Secondary:<br>Not reported |
| Monami et al.[25] (2008)<br><br>Metformin<br><br>vs<br><br>sulfonylureas, | MA<br><br>Patients with type 2 diabetes mellitus | N=7,890 (27 RCT)<br><br>Variable duration | Primary:<br>Reduction in $HbA_{1c}$ at 16 to 36 months<br><br>Secondary:<br>Not reported | Primary:<br>Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in $HbA_{1c}$ by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.<br><br>In direct comparisons, sulfonylureas led to a greater reduction in $HbA_{1c}$ (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists | | | | sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.<br><br>Secondary:<br>Not reported |
| **Type 2 Diabetes – Combination Therapy** | | | | |
| Buse et al.[26]<br><br>Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>vs<br><br>placebo<br><br>All patients also received optimized insulin glargine dosing (at randomization, patients with $HbA_{1c}$ levels >8.0% continued to receive current insulin glargine dose; those with $HbA_{1c}$ ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL). | DB, MC, PC, RCT<br><br>Type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, $HbA_{1c}$ 7.1 to 10.5%, BMI ≤45 kg/m$^2$, and stable body weight over past 3 months | N=261<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ ≤7.0 or ≤6.5%; seven-point self-monitored glucose concentrations; change in baseline body weight, waist circumference, and insulin dose; safety | Primary:<br>Exenatide significantly decreased $HbA_{1c}$ compared to placebo (-1.74 vs -1.04%; P<0.001).<br><br>Secondary:<br>A significantly greater proportion of patients receiving exenatide achieved an $HbA_{1c}$ ≤7.0% (60 vs 35%; treatment difference, 25%; 95% CI, 12 to 39; P<0.001). Similar results were observed with $HbA_{1c}$ ≤6.5% (40 vs 12%; treatment difference, 28%; 95% CI, 17 to 39; P<0.001).<br><br>With regards to seven-point self-monitored glucose concentrations, exenatide significantly decreased concentrations during morning and evening time points compared to placebo (P<0.001), but not at midday (P=0.320).<br><br>Exenatide significantly decreased body weight compared to placebo (-1.8 vs 1.0 kg; P<0.001), but no difference between treatments was observed in waist circumference (P=0.23).<br><br>The number of hypoglycemic events per-participant per-year did not differ between the exenatide and placebo (P=0.49). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Rosenstock et al.[27] (2012)<br><br>Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>vs<br><br>placebo<br><br>All patients also received optimized insulin glargine dosing (at randomization, patients with $HbA_{1c}$ levels >8.0% continued to receive current insulin glargine dose; those with $HbA_{1c}$ ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL). | Exploratory analysis of Buse et al.[26]<br><br>Baseline factors associated with glycemic control and weight loss in type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, $HbA_{1c}$ 7.1 to 10.5%, BMI ≤45 kg/m$^2$, and stable body weight over past 3 months | N=259<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$, weight<br><br>Secondary:<br>Not reported | Primary:<br>Patients receiving exenatide had achieved significantly greater reductions in $HbA_{1c}$ compared to patients receiving placebo, irrespective of baseline $HbA_{1c}$ (P<0.001).<br><br>Patients receiving exenatide with longer duration of diabetes and those with lower BMI achieved significantly greater reductions in $HbA_{1c}$ compared to patients receiving placebo (P<0.01).<br><br>Patients receiving exenatide lost significantly more weight, regardless of baseline $HbA_{1c}$ or BMI compared to patients receiving placebo (P<0.05).<br><br>Patients receiving exenatide with longer duration of diabetes lost the most weight compared to patients receiving placebo (P<0.001).<br><br>Secondary:<br>Not reported |
| Okerson et al.[28] (2010)<br><br>Exenatide 5 µg SC | Post-hoc analysis (6 RCTs)<br><br>Type 2 diabetics | N=2,171<br><br>24 to 52 weeks | Primary:<br>Change in baseline BP and pulse pressure | Primary:<br>In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, |

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| BID for 4 weeks, followed by 10 µg SC BID<br><br>vs<br><br>placebo or insulin<br><br>All patients also received existing antidiabetic treatment regimens. | ≥18 years of age with $HbA_{1c}$ ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m$^2$, and stable body weight | | Secondary:<br>Not reported | -2.80±0.75 mm Hg; P=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; P=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; P=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported).<br><br>Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001).<br><br>By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of "abnormal DBP" to "normal DBP" compared to placebo (treatment difference, 41.4 vs 32.4%; P=0.02).<br><br>Secondary:<br>Not reported |
| Buse et al.[29] (2004)<br><br>Exenatide 5 µg BID and | MC, PC, PG, RCT, TB<br><br>Type 2 diabetic patients 22 to 76 | N=377<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary: | Primary:<br>Significantly greater decreases in $HbA_{1c}$ were noted with exenatide 10 (-0.86%) and 5 µg (-0.46%) compared to placebo (0.12%; P<0.0002 for pairwise comparison). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| sulfonylurea (existing therapy)<br><br>vs<br><br>exenatide 10 µg BID and sulfonylurea (existing therapy)<br><br>vs<br><br>sulfonylurea (existing therapy) and placebo | years of age, treated with maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months, FPG <240 mg/dL, BMI 27 to 45 kg/m$^2$, $HbA_{1c}$ 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value | | Change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipoproteins | Secondary:<br>A significantly greater decreases in FPG was reported with exenatide 10 µg at week 30 compared to placebo (-0.6 vs 0.4 mmol/L; P<0.05). There was no difference between exenatide 5 µg and placebo (P value not reported).<br><br>A significantly greater decrease in body weight was noted with exenatide 10 µg at week 30 compared placebo (-1.6 vs -0.6 kg; P<0.05). There was no difference between exenatide 5 µg and placebo (P value not reported).<br><br>There were no differences in fasting insulin concentrations between any of the treatments (P value not reported).<br><br>A significantly greater decrease in fasting proinsulin concentrations was noted with exenatide 10 µg at week 30 compared to placebo (-16 mmol/L; P<0.01). A similar trend was reported with exenatide 5 µg compared to placebo, but no significance was reported (P value not reported).<br><br>There was a small decrease in LDL-C and apo B (P<0.05 for pairwise comparisons for both values) with exenatide compared to placebo. No differences were observed in other lipid parameters evaluated (P values not reported).<br><br>Side effects reported by patients receiving exenatide 10 µg included nausea (51%), vomiting (13%), diarrhea (9%), constipation (9%), and hypoglycemia (36%) (P values not reported).<br><br>There were 13 (10.1%) withdrawals due to adverse event(s) with exenatide 10 µg compared to nine (7.2%) withdrawals with exenatide 5 µg and four (3.3%) withdrawals with placebo (P values not reported). The majority of the events reported were mild to moderate in nature. Serious adverse events were reported in 4, 3, and 8% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo. Such events included a MI in an exenatide-treated patient and one placebo-treated patient who experienced clinical manifestations of coronary artery disease. |
| DeFronzo et al.[30] (2005)<br><br>Exenatide 5 µg | MC, PC, PG, RCT, TB<br><br>Type 2 diabetic | N=336<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>Significantly greater decreases in $HbA_{1c}$ were reported with exenatide 10 (-0.78%) and 5 µg (-0.40%) compared to placebo (0.08%; P<0.002 for pairwise comparison). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| BID and metformin (existing therapy)<br><br>vs<br><br>exenatide 10 µg BID and metformin (existing therapy)<br><br>vs<br><br>metformin (existing therapy) and placebo | patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m$^2$, $HbA_{1c}$ 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value | | Secondary:<br>Proportion of patients achieving $HbA_{1c}$ ≤7.0%; change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipids | Secondary:<br>A significantly greater proportion of patients achieved $HbA_{1c}$≤7.0% with exenatide 5 (27%) and 10 µg (40%) compared to placebo (11%; P<0.01 for pairwise comparison).<br><br>Significantly greater decreases in FPG were observed with exenatide 5 (-7.2 mg/dL; P<0.005) and 10 µg (-10.1 mg/dL; P<0.0001) compared to placebo (14.4 mg/dL).<br><br>Significantly greater decreases in body weight were observed with exenatide 5 (-1.6 kg; P<0.05) and 10 µg (-2.8 kg; P<0.001) compared to placebo (-0.3 kg).<br><br>There was no difference in fasting insulin or proinsulin concentrations between any of the treatments (P values not reported).<br><br>No differences in lipid profiles were observed between any of the treatments (P value not reported).<br><br>Gastrointestinal side effects were most commonly reported with exenatide and included nausea (45%), diarrhea (16%), and vomiting (12%) in exenatide 10 µg-treated patients (P values not reported).<br><br>The incidence of hypoglycemia was similar with all treatments. Withdrawals due to adverse event(s) occurred in 7.1, 3.6, and 0.9% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported). |
| Kendall et al.[31] (2005)<br><br>Exenatide 5 µg BID and oral hypoglycemic therapy (existing therapy)<br><br>vs | DB, MC, PC, PG, RCT<br><br>Type 2 diabetic patients 22 to 77 years of age, treated with maximally effective doses of metformin (≥1,500 mg/day) and a sulfonylurea (4 | N=733<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, PPG, and body weight | Primary:<br>Significantly greater decreases in $HbA_{1c}$ were achieved with exenatide 5 (-0.55±0.07%) and 10 µg (-0.77±0.08%) compared to placebo (0.23±0.07%; P<0.001 for pairwise comparison).<br><br>Secondary:<br>Significantly greater decreases in FPG were achieved with exenatide 5 (-0.5±0.2 mmol/L) and 10 µg (-0.6±0.2 mmol/L) compared to placebo (0.8±0.2 mmol/L; P<0.0001 for pairwise comparison).<br><br>Significantly greater decreases in PPG were achieved with exenatide 5 |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| exenatide 10 µg BID and oral hypoglycemic therapy (existing therapy)<br><br>vs<br><br>oral hypoglycemic therapy (existing therapy) and placebo | mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) for ≥3 months before screening, FPG <13.3 mmol/L, BMI 27 to 45 kg/m$^2$, $HbA_{1c}$ 7.5 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value | | | (P=0.009) and 10 µg (P=0.0004) compared to placebo.<br><br>Significantly greater decreases in body weight were achieved with exenatide 5 (-1.6±0.2 kg) and 10 µg (-1.6±0.2 kg) compared to placebo (-0.9±0.2 kg; P≤0.01).<br><br>Nausea was the most commonly reported adverse event and was observed in 48.5, 39.2, and 20.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported). A higher incidence of hypoglycemia was reported with exenatide. Hypoglycemia was reported in 27.8, 19.2, and 12.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported). |
| Zinman et al.[32] (2007)<br><br>Exenatide 5 µg BID for 4 weeks followed by 10 µg BID<br><br>vs<br><br>placebo<br><br>All patients | MC, PC, RCT<br><br>Type 2 diabetics 21 to 75 years of age with a stable dose of a TZD (rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day) for ≥4 months before screening, alone or in combination with | N=233<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, body weight, self-monitored blood glucose concentrations, safety | Primary:<br>Exenatide significantly decreased $HbA_{1c}$ compared to placebo (-0.89±0.09 vs 0.09±0.10%; P<0.001).<br><br>Secondary:<br>Exenatide significantly decreased FPG compared to placebo (-1.59±0.22 vs 0.10±0.21 mmol/L; P<0.001).<br><br>Exenatide significantly decreased weight compared to placebo (treatment difference, -1.51 kg; P<0.001).<br><br>Exenatide-treated patients achieved significantly decreased self-monitored blood glucose profiles at each measurement throughout the day at week 16 |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| received existing TZD regimen, with or without metformin. | a stable dose of metformin for 30 days, $HbA_{1c}$ 7.1 to 10.0%, BMI 25 to 45 kg/m$^2$, and a history of stable body weight (≤10% variation) for ≥3 months before screening | | | compared to baseline (P<0.001) and placebo treated patients (P<0.001).<br><br>Adverse events that were reported more commonly with exenatide included nausea (39.7 vs 15.2%; 95% CI, 12.7 to 36.3), vomiting (13.2 vs 0.9%; 95% CI, 5.2 to 19.5), and dyspepsia (7.4 vs 0.9%; 95% CI, 0.7 to 12.4). |
| Ratner et al.[33] (2006)<br><br>Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>All patients also received existing metformin therapy. | ES, MC, OL<br><br>Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m$^2$, $HbA_{1c}$ 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value | N=150<br><br>52 weeks (82 weeks total) | Primary:<br>Changes in baseline $HbA_{1c}$, body weight, and lipid profile of the completer cohort (those patients who completed 82 weeks of exenatide) and total cohort (ITT population)<br><br>Secondary:<br>Proportion of patients in the completer cohort with baseline $HbA_{1c}$ >7.0% who achieved an $HbA_{1c}$ ≤7.0%, reduction of weight after stratification by baseline BMI, safety | Primary:<br>At week 30, the completer cohort had significant decreases in $HbA_{1c}$ from baseline of -1.0±0.1%. At week 82, the decrease was -1.3±0.1% (95% CI, -1.5 to -1.0; P<0.05). For the total cohort, the decrease at week 30 was -0.7±0.1% (95% CI, -0.8 to -0.5; P<0.05) and at week 82 was -0.8±0.1% (95% CI, -1.0 to -0.6; P<0.05).<br><br>At week 30, the completer cohort had significant decreases in body weight from baseline of -3.0±0.6 kg. At week 82, the decrease from baseline was -5.3±0.8 kg (95% CI, -7.0 to -3.7; P<0.05). For the total cohort, the decrease at week 30 was -2.3±0.4 kg and at week 82 was -4.3±0.6 kg (95% CI, -5.5 to -3.2; P<0.05).<br><br>At week 82, the completer cohort experienced significant decreases in apo B (-5.20 mg/dL; 95% CI, -10.00 to -0.22; P value not reported), a reduction in TG (-73 mg/dL; 95% CI, -107 to -39; P value not reported) and an increase in HDL-C (4.5 mg/dL; 95% CI, 2.3 to 6.6; P value not reported).<br><br>Secondary:<br>At weeks 30 and 82, the proportion of patients in the completer cohort whose baseline $HbA_{1c}$ was >7.0% and who achieved an $HbA_{1c}$ ≤7.0% was 46 and 59% (P values were not reported).<br><br>Patients in the completer cohort whose baseline BMI ≥30 kg/m$^2$ experienced a greater decrease of weight (-6.9±1.1 kg) compared to those whose baseline BMI was <30 kg/m$^2$ (-2.3±0.8 kg; P values were not reported).<br><br>The following adverse events were experienced by patients in the total |

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| | | | | cohort: nausea (14 to 33%), upper respiratory tract infections (3 to 10%), diarrhea (3 to 7%), vomiting (1 to 5%), and dizziness (2 to 6%) (P values were not reported). |
| Riddle et al.[34] (2006)<br><br>Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>All patients also received existing metformin and sulfonylurea therapies. | ES, MC, OL<br><br>Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) or maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months before screening, FPG <240 mg/dL, BMI of 27 to 45 kg/m$^2$, $HbA_{1c}$ 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value | N=401<br><br>52 weeks (82 weeks total) | Primary:<br>Change in baseline $HbA_{1c}$ and FPG in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population)<br><br>Secondary:<br>Change in baseline weight, change in baseline $HbA_{1c}$ and weight stratified by baseline $HbA_{1c}$ and BMI | Primary:<br>At week 30, the completer cohort experienced a significant decrease in $HbA_{1c}$ of -0.8±0.1% for the original exenatide 5 µg arm and -1.0±0.1% for the original 10 µg arm. At week 82, the decrease was -1.0±0.1% (95% CI, -0.9 to -1.2; P value not reported). For the total cohort group, the decrease at week 82 was -0.7±0.1% (95% CI, -0.8 to -0.5; P value not reported). Results from week 30 week were not reported.<br><br>At week 30, the completer cohort observed a decrease in FPG of -0.52±0.16 mmol/L (P value not reported). At week 82, the decrease was -0.62±0.19 mmol/L (P value not reported). FPG data for the total cohort were not reported.<br><br>Secondary:<br>At week 30, the completer cohort group experienced a decrease in body weight of -1.4±0.3 kg for the original exenatide 5 µg arm and -2.1±0.3 kg for the original 10 µg arm. At week 82, the decrease was -4.0±0.3 kg (95% CI, -4.6 to -3.4). The total cohort experienced a decrease in body weight of -3.3±0.2 kg (95% CI, -2.8 to -3.7; P value not reported).<br><br>At week 82, patients in the completer cohort who had a baseline BMI ≥30 kg/m$^2$ experienced a greater decrease in mean weight from baseline of -4.4±0.4 kg compared to -3.2±0.5 kg in patients with a baseline BMI <30 kg/m$^2$ (P values not reported).<br><br>Of the patients in the completer cohort who had a baseline $HbA_{1c}$ >7.0%, 44% achieved an $HbA_{1c}$ ≤7.0% at week 82. Patients with a baseline $HbA_{1c}$ ≥9.0% experienced a greater decrease (-1.9±0.2%) compared to those with a baseline $HbA_{1c}$<9.0% (-0.7±0.1%) (P values were not reported).<br><br>The most common reasons for withdrawal were administrative (study site closure) (12%), withdrawal of consent (11%), and adverse events (7%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 27% and 8 to 15% of patients, respectively (P values not reported). |

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| Blonde et al.[35] (2006)<br><br>Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>All patients also received existing metformin and sulfonylurea therapies. | IA, MC, OL<br><br>Type 2 diabetics | N=551<br><br>52 weeks (82 weeks total) | Primary:<br>Change in baseline $HbA_{1c}$ and safety in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population)<br><br>Secondary:<br>Change in baseline FPG and weight, change in baseline weight and $HbA_{1c}$ stratified by baseline BMI and $HbA_{1c}$, change in lipid profile | Primary:<br>At week 30, the completer cohort experienced a significant decrease in $HbA_{1c}$ of -0.9±0.1%, and this decrease was maintained at week 82, with a decrease of -1.1±0.1% (95% CI, -1.0 to -1.3; P value not reported). The total cohort experienced a decrease at week 82 of -0.8±0.1% (95% CI, -0.6 to -0.9; P value not reported).<br><br>Of the 551 ITT population, 314 (57%) patients completed the ES. Reasons for withdrawal included withdrawal of consent (11%), adverse events (7%), loss of glucose control (4%), and other (21%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 29% and 7 to 12% of patients, respectively (P values not reported).<br><br>Secondary:<br>At week 30, the completer cohort experienced a decrease in FPG of -0.7±0.1 mmol/L (P value not reported). At week 82, the decrease was -0.9±0.2 mmol/L (P value not reported). The total cohort FPG levels were not reported.<br><br>At week 30, the completer cohort group experienced a decrease in body weight of -2.1±0.2 kg and at week 82 the decrease was -4.4±0.3 kg (95% CI, -3.8 to -5.1; P value not reported). At week 82, the total cohort experienced a decrease in body weight of -3.5±0.2 kg (95% CI, -3.1 to -4.0; P value not reported).<br><br>At week 82, patients in the completer cohort who had a baseline BMI ≥40 $kg/m^2$ experienced a decrease of -7 kg compared to -2 kg in patients with a baseline BMI <25 $kg/m^2$ (P values not reported).<br><br>In the completer cohort, of those patients whose baseline $HbA_{1c}$ was >7.0%, 39 and 48% achieved $HbA_{1c}$ ≤7.0% at weeks 30 and 82, respectively. At week 82, a greater decrease in $HbA_{1c}$ was achieved in patients who had a baseline $HbA_{1c}$ ≥9.0% (-2.0±0.2) compared to those with a baseline $HbA_{1c}$ <9.0% (-0.8±0.1) (P values were not reported).<br><br>In the completer cohort, of the lipid levels measured, significant benefits were observed in HDL-C (4 mg/dL; 95% CI, 3.7 to 5.4) and TG (-38.6 mg/dL; 95% CI, -55.5 to -21.6) at week 82 (P values not reported). |

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| Buse et al.[36] (2007)<br><br>Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>All patients also received existing metformin and sulfonylurea therapies. | IA, OL<br><br>Type 2 diabetics | N=521<br><br>104 weeks (2 years total) | Primary:<br>Change in baseline $HbA_{1c}$, weight, and hepatic biomarkers; safety<br><br>Secondary:<br>Not reported | Primary:<br>At week 104, exenatide significantly decreased $HbA_{1c}$ by -1.1% (95% CI, -1.3 to -1.0; P<0.001).<br><br>At week 104, exenatide significantly decreased weight by -4.7 kg (95% CI, -5.4 to -4.0; P<0.001).<br><br>At Week 104, exenatide significantly decreased ALT by -5.3 IU/L (95% CI, -7.1 to -3.5; P<0.05) and decreased AST by -2.0 IU/L (95% CI, -3.3 to -0.8; P<0.05).<br><br>Adverse events with an overall incidence ≥10% during 104 weeks of treatment were reported with the following proportion of patients affected: nausea (8 to 39%), upper respiratory tract infections (2 to 10%), and hypoglycemia (<1 to 13%) (P values were not reported).<br><br>Secondary:<br>Not reported |
| Klonoff et al.[37] (2008)<br><br>Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>All patients also received existing metformin and sulfonylurea therapies. | IA, OE, OL<br><br>Type 2 diabetics | N=217<br><br>156 weeks (3 years total) | Primary:<br>Change in baseline $HbA_{1c}$, weight, and ALT; safety<br><br>Secondary:<br>Not reported | Primary:<br>At Week 156, exenatide significantly decreased $HbA_{1c}$ by -1.0±0.1% (P<0.0001).<br><br>At Week 156, exenatide significantly decreased weight by -5.3±0.4 kg (P<0.0001).<br><br>At Week 156, exenatide significantly decreased ALT by -10.4±1.5 IU/L in patients with elevated ALT at baseline (P<0.0001).<br><br>The most frequently reported adverse event was mild to moderate nausea.<br><br>Secondary:<br>Not reported |
| Viswanathan et al.[38] (2007)<br><br>Exenatide 5 µg SC BID | RETRO<br><br>Obese type 2 diabetic patients not adequately controlled despite | N=52<br><br>26 weeks | Primary:<br>Change in baseline body weight, $HbA_{1c}$, and insulin dose | Primary:<br>Exenatide-treated patients experienced a significant decrease in body weight of -6.46±0.80 kg (P<0.001) compared to the patients in the control group who experienced a significant weight gain of 2.4±0.6 kg (P<0.001).<br><br>Exenatide-treated patients experienced a decrease in $HbA_{1c}$ (-0.60±0.21%; |

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| vs<br><br>control group (patients who discontinued exenatide therapy within 2 weeks on initiation due to insurance-related, personal or economic reasons)<br><br>The dosages of rapid-acting and mixed insulin were reduced by 10% in patients with $HbA_{1c}$ <7.5%.<br><br>Subsequent dosage adjustments were made carefully based on ambient glucose concentrations. | treatment with oral hypoglycemic agents and insulin and $HbA_{1c}$ >7.0% | | Secondary:<br>Change in baseline TC, TG, DBP, SBP, and high-sensitivity CRP; safety | P=0.007). The patients in the control group also experienced a decrease in $HbA_{1c}$ (-8.4±0.5%; P value not reported).<br><br>Exenatide-treated patients experienced a significant decrease in rapid-acting insulin requirements from 50.4±6.7 to 36.6±5.1 units (P<0.02) and for mixed insulin from 72.9±15.6 to 28.3±14.8 units (P<0.02). Insulin requirements for the control group were not reported.<br><br>Secondary:<br>Exenatide-treated patients experienced a significant decrease in TC from 163.9±8.2 to 149.8±5.9 mg/dL (P=0.03) compared to the patients in the control group who experienced a decrease from 168.1±16.3 to 144.33±10.39 mg/dL (P=0.08).<br><br>Exenatide-treated patients experienced a significant decrease in TG from 202.5±28.8 to 149.9±17.3 mg/dL (P=0.01) compared to the patients in the control group who experienced a decrease from 182.7±23.9 to 171.1±39.2 mg/dL (P=0.91).<br><br>Exenatide-treated patients experienced a significant decrease in SBP of -9.2±3.3 mm Hg (P=0.02). Data for the control group were not reported. Neither group experienced a reduction in DBP.<br><br>Exenatide-treated patients experienced a significant decrease in high-sensitivity CRP of -34.0±14.3% (P=0.05). Data for the control group were not reported.<br><br>Four patients receiving exenatide experienced severe nausea during treatment which led to discontinuation. Mild nausea was experienced by several other patients that did not interfere with therapy. Hypoglycemia (glucose <60 mg/dL) was rare and did not lead to any hospital admissions. No other adverse events were observed. |
| Marre et al.[39] (2009)<br>LEAD-1<br><br>Liraglutide 0.6, 1.2, and 1.8 mg SC | AC, DB, DD, MC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age treated | N=1,041<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of | Primary:<br>After 26 weeks, $HbA_{1c}$ decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; |

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| QD plus glimepiride 2 to 4 mg/day and placebo<br><br>vs<br><br>placebo plus glimepiride 2 to 4 mg/day<br><br>vs<br><br>placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day | with an oral glucose-lowering agent for ≥3 months, $HbA_{1c}$ 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m$^2$ | | patients reaching $HbA_{1c}$ (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP | P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in $HbA_{1c}$ were greater in patients previously on an oral glucose lowering agent monotherapy.<br><br>Secondary:<br>The proportion of patients reaching $HbA_{1c}$ targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached $HbA_{1c}$ <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching $HbA_{1c}$ targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018).<br><br>The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).<br><br>The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported).<br><br>Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported).<br><br>Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR. |

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| | | | | Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported). |
| Nauck et al.[40] (2009)<br>LEAD-2<br><br>Liraglutide 0.6, 1.2, and 1.8 mg SC QD<br><br>vs<br><br>placebo<br><br>vs<br><br>glimepiride 4 mg/day<br><br>All patients also received metformin 1,500 to 2,000 mg/day. | AC, DB, DD, MC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age with $HbA_{1c}$ 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m$^2$ | N=1,091<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Changes in baseline body weight, FPG, seven-point self-monitored glucose concentrations, and β cell function | Primary:<br>$HbA_{1c}$ decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had more efficacious glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in $HbA_{1c}$ between liraglutide and glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride.<br><br>Secondary:<br>Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; P≤0.01).<br><br>Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; P value not reported).<br><br>Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; P<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (P values not reported).<br><br>No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (P values not reported).<br><br>Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (P value not reported), and were significantly |

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| | | | | greater compared to placebo (0.1; P<0.0001).<br><br>Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (P values not reported). |
| Zinman et al.[41] (2009)<br>LEAD-4<br><br>Liraglutide 1.2 and 1.8 mg SC QD<br><br>vs<br><br>placebo<br><br>All patients also received metformin 2,000 mg/day and rosiglitazone 8 mg/day. | DB, MC, PC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age with $HbA_{1c}$ 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy for ≥3 months), and BMI ≤45 kg/m$^2$ | N=533<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline body weight, FPG, seven-point self-monitored glucose concentrations, β cell function, and lipids | Primary:<br>The mean baseline $HbA_{1c}$ for the overall population decreased by -1.5±0.1% with liraglutide 1.2 (95% CI, -1.1 to -0.8; P value not reported) and 1.8 mg (95% CI, -1.1 to -0.8; P value not reported) compared to -0.5±0.1% with placebo.<br><br>Secondary:<br>Weight loss with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -1.0±0.3 kg and liraglutide 1.8 mg, -2.0±0.3 kg; P<0.0001 for both).<br><br>Decreases in FPG with liraglutide (liraglutide 1.2 mg, -2.2 mmol/L and liraglutide 1.8 mg, -2.4 mmol/L) were significantly greater compared to placebo (-0.4 mmol/L; P<0.0001 for both).<br><br>Decreases in mean PPG were significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, -2.6 mmol/L; liraglutide 1.8 mg, -2.7 mmol/L; and placebo, -0.8 mmol/L; P<0.001 for both).<br><br>The decrease in proinsulin:insulin ratio with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -0.029±0.026; liraglutide 1.8 mg -0.085±0.260; placebo, 0.036±0.029; P<0.05 for both).<br><br>The increase in C-peptide was significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, 131±32; liraglutide 1.8 mg, 144±31; placebo, 51±34 pmol/L; P<0.05 for both).<br><br>Increases in HOMA-B with liraglutide were significantly greater compared to placebo (P<0.05), but decreases with HOMA-IR were not different between treatments (P values not reported).<br><br>Decreases in FFA were significantly greater with liraglutide 1.2 mg (- |

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| | | | | 0.03±0.02 mmol/L; P<0.05) and liraglutide 1.8 mg (-0.05±0.02 mmol/L; P<0.05) compared to placebo (0.02±0.02). Other significant decreases in lipid profiles with liraglutide compared to placebo were LDL-C (liraglutide 1.2 mg, -0.28±0.07 vs -0.10±0.07 mmol/L; P<0.05) and TG (liraglutide 1.2 mg, -0.38±0.10 vs -0.13±0.11 mmol/L; P<0.05). |
| Russell-Jones et al.[42] (2009) LEAD-5<br><br>Liraglutide 1.8 mg SC QD<br><br>vs<br><br>placebo<br><br>vs<br><br>insulin glargine (OL)<br><br>All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day. | PC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥3 months before screening, $HbA_{1c}$ 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m$^2$ | N=581<br><br>26 weeks | Primary:<br>Change in baseline in $HbA_{1c}$<br><br>Secondary:<br>Change in baseline body weight, waist circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP | Primary:<br>Decreases in $HbA_{1c}$ were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015).<br><br>Secondary:<br>The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001).<br><br>The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608).<br><br>Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported).<br><br>Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported).<br><br>Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, - |

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| | | | | 0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide.<br><br>A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; P=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin. |
| Kaku et al.[43] (2010)<br><br>Liraglutide 0.6 and 0.9 mg SC QD<br><br>vs<br><br>placebo<br><br>All patients received existing sulfonylurea therapy. | DB, MC, PG, RCT<br><br>Japanese type 2 diabetics ≥20 years of age currently treated with a sulfonylurea for ≥8 weeks, $HbA_{1c}$ 7.0 to <10.0%, and BMI <35 kg/$m^2$ | N=264<br><br>52 weeks (initial 24 week DB period, followed by 28 week OL period to assess the long-term safety and efficacy of liraglutide) | Primary:<br>Change in baseline $HbA_{1c}$ at 24 weeks<br><br>Secondary:<br>seven-point self-monitored glucose concentrations, body weight, FPG, PPG, lipid profile, biomarkers for cardiovascular effects, proportion of patients reaching an $HbA_{1c}$ <7.0 or <6.5% (post-hoc analysis) | Primary:<br>Liraglutide significantly decreased and sustained $HbA_{1c}$ compared to placebo. The decrease at week 24 was greater with liraglutide 0.9 mg (-1.56±0.84%) compared to the other treatments (liraglutide 0.6 mg, -1.46±0.95% and placebo, -0.40±0.93%). $HbA_{1c}$ at week 24 were significantly lower with liraglutide compared to placebo (7.02 and 6.75% with liraglutide 0.6 and 0.9 mg compared to 8.02% with placebo) with the treatment differences of -1.00% (95% CI, -1.24 to -0.75) with liraglutide 0.6 mg and -1.27% (95% CI, -1.51 to -1.02) with liraglutide 0.9 mg.<br><br>Secondary:<br>Improvements in metabolic controls were apparent in the seven-point self monitored glucose concentration profiles at week 24, with significant reductions in glucose. Plasma glucose was significantly lower with liraglutide compared to placebo (P<0.0001).<br><br>Body weight did not change with liraglutide (0.6 mg, 0.06 kg and 0.9 mg, -0.37 kg) despite the improvements seen in glycemic control (P values not reported). Weight decreased with placebo (-1.12 kg).<br><br>Full impact on FPG levels was achieved at the first two visits at week four, and levels were significantly lower with liraglutide at week 24 compared to placebo. FPG with liraglutide 0.6 and 0.9 mg was significantly lower compared to placebo (7.34±0.19, 7.01±0.19, and 8.81±0.19 mmol/L, respectively; P<0.0001). The estimated means of PPG at week 24 at all time points with liraglutide were lower compared to placebo, with much lower mean values occurring with liraglutide 0.9 mg (P values not reported). The means of $AUC_{0\text{-}3hr}$ at week 24 were also significantly lower with liraglutide |

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| | | | | compared to placebo (P<0.0001).<br><br>No significant treatment effects were observed in any of the parameters of the lipid profile. The cardiovascular biomarker BNP was significantly lower with liraglutide compared to placebo (liraglutide 0.6 mg vs placebo; P=0.0018 and liraglutide 0.9 mg vs placebo; P=0.0157). High-sensitivity CRP was significantly lower with liraglutide 0.6 mg compared to placebo (P=0.0218), but no difference was observed between liraglutide 0.9 mg and placebo (P=0.8143). No treatment effect was seen in the estimated mean of PAI-1 at week 24 (P values not reported).<br><br>A significantly greater proportion of patients receiving liraglutide achieved $HbA_{1c}$ values <7.0 and <6.5% compared to placebo (P values not reported). |
| Drucker et al.[44] (2008) DURATION-1<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>exenatide 5 µg SC BID for 28 days, followed by 10 µg BID | AC, OL, NI, RCT<br><br>Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; $HbA_{1c}$ 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m$^2$; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents | N=303<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Safety and tolerability; FPG and PPG; body weight; fasting glucagon; fasting lipids; BP; proportion of patients achieving $HbA_{1c}$ ≤7.0, ≤6.5, and ≤6.0%; exenatide antibodies | Primary:<br>Both treatments achieved significant decreases in $HbA_{1c}$, with a decrease at week 30 of -0.33±0.10% (95% CI, -0.54 to -0.12). Decreases were significantly greater with exenatide ER compared to exenatide (-1.9±0.1 vs -1.5±0.1%; P=0.0023). Significant decreases with both treatments were observed as early as week six, and the mean decrease was significantly greater with exenatide ER compared to exenatide by week 10, and the difference persisted throughout the remainder of the trial. Overall, decreases were consistent across all treatment background therapies and did not vary notably with sex or age (>65 years vs <65 years).<br><br>Secondary:<br>Adverse events reported in >10% of patients include nausea (26.4 vs 34.5%), vomiting (10.8 vs 18.6%), injection site pruritis (17.6 vs 1.4%), upper respiratory tract infection (8.1 vs 17.2%), diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), injection site bruising (4.7 vs 10.3%), and urinary tract infection (10.1 vs 8.3%). Gastrointestinal complaints were the most frequently reported adverse events with exenatide. Treatment-related nausea was reported in significantly fewer patients receiving exenatide ER (P value not reported). Reported nausea with both treatments was predominantly mild in intensity, and no severe nausea was reported with exenatide ER. Injection site pruritis with either treatment was typically mild in intensity, and resolved with continued treatment. No episodes of major hypoglycemia were reported with either treatment, and the incidence of minor hypoglycemia was low. Withdrawals due to adverse events were 6.1 vs 4.8% (P value not |

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| | | | | reported). No clinically significant abnormalities in vital signs; electrocardiogram reports; or hematological, chemistry, or urinalysis values were reported. The incidence of serious adverse events was low (5.4 vs 3.4%). No cases of pancreatitis were reported with either treatment.<br><br>Both treatments achieved significant decreases in FPG and PPG, with exenatide ER achieving significantly greater decreases in FPG compared to exenatide (-2.3±0.2 vs -1.4±0.2 mmol/L; 95% CI, -1.3 to -5.2; P<0.0001). Analysis across all background treatments revealed similar results. Similar results were observed with PPG (data reported in graphical form only). Both treatments resulted in significant improvements in 7-point self-monitored glucose concentrations profiles.<br><br>Body weight decreased progressively with both treatments (-3.7±0.5 vs -3.6±0.5 kg; 95% CI, -1.3 to 1.1; P=0.89). At week 30, the mean percentage of weight loss from baseline was -3.6 vs -3.7% with exenatide ER and exenatide (P>0.05).<br><br>Both treatments significantly decreased FPG and PPG (P values not reported).<br><br>Exenatide ER achieved significantly greater decreases in TC (-0.31±0.06 vs -0.10±0.06 mmol/L) and LDL-C (-0.13±0.05 vs 0.03±0.05 mmol/L) compared to exenatide (P values not reported). TG decreased with both treatments (-15 vs -11%; P value not reported).<br><br>Both treatments achieved significant improvements in SBP and DBP (P values not reported).<br><br>A significantly greater proportion of patients receiving exenatide ER achieved an $HbA_{1c}$ ≤7.0% compared to patients receiving exenatide (77 vs 61%; P=0.0039). Forty nine and 25% of patients receiving exenatide ER achieved $HbA_{1c}$ ≤6.5 and ≤6.0%.<br><br>Anti-exenatide antibody levels were significantly higher with exenatide ER compared to exenatide (P=0.0002), but most antibodies were either not detectable or of low titer. |
| Buse et al.[45] | ES (DURATION- | N=258 | Primary: | Primary: |

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| (2010)<br>DURATION-1<br><br>Exenatide ER 2 mg SC once weekly (continued exenatide ER)<br><br>vs<br><br>exenatide ER 2 mg SC once weekly (switched to exenatide ER)<br><br>Patients enrolled in DURATION-1 who were randomized to exenatide 10 µg SC BID were transitioned to exenatide ER 2 mg SC once weekly after the initial 30 week trial period. | 1[44])<br><br>Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; $HbA_{1c}$ 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m$^2$; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents | 22 weeks (52 weeks total) | Efficacy, body weight, glucose control, lipid and BP profile, safety and tolerability<br><br>Secondary:<br>Not reported | During the 22 weeks, patients who continued exenatide ER maintained improvements in $HbA_{1c}$, with a decrease of -2.1% (95% CI, -2.2 to -1.9) at week 30 and -2.0% (95% CI, -2.1 to -1.8) at week 52. Patients who switched to exenatide ER (week 30 $HbA_{1c}$ decrease, -1.8%; 95% CI, -1.9 to -1.6) exhibited further improvements in glycemic control and achieved the same reduction (-2.0%) and mean $HbA_{1c}$ (6.6%) at week 52 compared to patients who continued exenatide ER. After 52 weeks, 71 and 54% of all patients achieved an $HbA_{1c}$ ≤7.0 and ≤6.5% (similar between the two cohorts). In patients with a baseline $HbA_{1c}$ <9.0%, the decrease at week 52 was -1.2 (95% CI, -1.4 to -1.1) and -1.3% (95% CI, -1.5 to -1.2) in patients who continued exenatide ER and in those who switched to exenatide ER. Larger decreases in $HbA_{1c}$ were observed in patients with a baseline $HbA_{1c}$ ≥9.0% (-2.8 [95% CI, -3.1 to -2.5] vs -2.6% [95% CI, -3.0 to -2.3]).<br><br>Body weight decreased similarly with both treatments. At week 52, the decreases in body weight were -4.1 (95% CI, -5.3 to -2.9) vs -4.5 kg (95% CI, -5.7 to -3.3) in patients who continued exenatide ER and those who switched to exenatide ER.<br><br>In patients who continued exenatide ER, the decreases in FPG achieved at week 30 (-46 mg/dL; 95% CI, -52 to -40) were maintained throughout the 52 weeks (-47 mg/dL; 95% CI, -53 to -41). Patients who switched to exenatide ER achieved a similar decrease in FPG at week 52 (-43 mg/dL; 95% CI, -49 to -37). Subsequent to week 30, patients switched to exenatide ER experienced a transient rise in mean FPG followed by a rapid decreases within two weeks after switching treatment.<br><br>Clinically significant improvements in BP were observed in patients who continued exenatide ER for 52 weeks. (SBP, -6.2 mm Hg; 95% CI, -8.5 to -3.9 and DBP, -2.8 mm Hg; 95% CI, -4.3 to -1.3) and in patients who switched to exenatide ER (SBP, -3.8 mm Hg; 95% CI, -6.1 to -1.5 and DBP, -1.8 mm Hg; 95% CI, -3.2 to -0.3). Fifty and 36% of patients in the two treatment groups who had elevated SBP at baseline achieved normal SBP at week 52. Improvements in lipid profiles were achieved in both treatment groups, with clinically significant decreased in TC (-9.6 [95% CI, -14.8 to -4.3] and -9.0 mg/dL [95% CI, -14.5 to -3.6]) and TG (-15%; 95% CI, -21 to -9). |

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| | | | | Treatment-emergent adverse events that occurred for the first time or worsened during the 22 week long second phase were similar to those observed during the initial 30 weeks of treatment. Nausea was predominantly mild, and no severe cases were reported. Twenty one patients (four vs 17) reported injection site-related adverse events. Mild to moderate injection site pruritis was observed after switching from exenatide to exenatide ER in six patients. No cases of pancreatitis were reported.<br><br>Secondary:<br>Not reported |
| Blevins et al.[46] (2011)<br>DURATION-5<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID | AC, MC, OL, RCT<br><br>Type 2 diabetics ≥18 years of age treated for ≥2 months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; $HbA_{1c}$ 7.1 to 11.0%; FPG <280 mg/dL; and BMI 25 to 45 $kg/m^2$ | N=252<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ <7.0 and <6.5% and FPG ≤126 mg/dL, body weight, FPG, BP, lipid profile, safety and tolerability | Primary:<br>Decreases in $HbA_{1c}$ were significantly greater with exenatide ER compared to exenatide (-1.6±0.1 vs -0.9±0.1%, treatment difference, -0.7%; 95% CI, -0.9 to -0.4). At week 24, $HbA_{1c}$ was 7.1±0.1 and 7.7±0.1% with exenatide ER and exenatide.<br><br>Secondary:<br>A significantly greater proportion of patients receiving exenatide ER achieved $HbA_{1c}$ <7.0 (58.1 vs 30.1%; P<0.0001) and <6.5% (41.1 vs 16.3%; P<0.0001) compared to exenatide. Similar results were achieved for FPG ≤126 mg/dL (50.4 vs 30.9%; P=0.0008).<br><br>Both treatments resulted in progressive decreases in body weight through 24 weeks (between group difference, -0.95 kg; 95% CI, -1.9 to 0.01). By week 24, 77 and 63% of patients receiving exenatide ER and exenatide experienced weight loss, whereas 71 and 51% of patients experienced both weight loss and a decrease in $HbA_{1c}$.<br><br>Decreases in FPG were significantly greater with exenatide ER compared to exenatide (-35±5 vs -12±5 mg/dL; P=0.0008).<br><br>Decreases in SBP were significant with exenatide ER (-2.9±1.1 mm Hg; 95% CI, -5.2 to -0.7), but not with exenatide. No significant decreases in DBP were observed with either treatment.<br><br>Decreases in TC (-15.4±2.6 mg/dL; 95% CI, -20.5 to -10.2) and LDL-C (-6.4±2.1 mg/dL; 95% CI, -10.7 to -2.2) were significant with exenatide ER, and no significant changes were observed with exenatide. |

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| | | | | Nausea, the adverse event most commonly reported with both treatments (14 vs 35%), occurred at a lower incidence in patients receiving exenatide ER. Injection site-related adverse events were more common with exenatide ER (13 vs 10%), with one patient receiving exenatide ER withdrawing from treatment due to mild injection site pruritis. There were no major hypoglycemic episodes. The incidences of serious adverse events were low (2 vs 4%). During the course of treatment there was substantial variability in pancreatic-amylase and lipase concentrations. The incidence of adverse events, including gastrointestinal symptoms was similar between patients with normal and abnormal post-baseline amylase and lipase measured at any post-baseline time point. |
| Buse et al.[47] (2009) LEAD-6<br><br>Liraglutide 1.8 mg SC QD<br><br>vs<br><br>exenatide 10 µg SC BID<br><br>Background oral glucose-lowering agents were maintained at pre-trial doses unless unacceptable hypoglycemia occurred, in which case sulfonylurea doses could be reduced to no less than 50% of the starting dose. | AC, MC, OL, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age with $HbA_{1c}$ 7.0 to 11.0%; BMI ≤45 kg/m$^2$; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months | N=464<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients reaching $HbA_{1c}$ targets (<7.0 and ≤6.5%); change in baseline FPG, seven-point self-monitored glucose concentrations, body weight, β cell function, glucagon, BP, and lipid profiles | Primary:<br>Decreases in $HbA_{1c}$ with liraglutide were more efficacious compared to exenatide (-1.12 vs -0.79%; treatment difference, -0.33; 95% CI, -0.47 to -0.18; P value not reported). Data in the ITT population demonstrated similar decreases with liraglutide and exenatide (-1.16 vs -0.87%; estimated treatment difference, -0.29%; 95% CI, -0.45 to -0.13; P<0.0001).<br><br>Secondary:<br>The proportion of patients achieving target $HbA_{1c}$ was significantly greater with liraglutide compared to exenatide ($HbA_{1c}$ <7.0%, 54 vs 43%; OR, 2.02; 95% CI, 1.31 to 3.11; P value not reported and $HbA_{1c}$ ≤6.5%, 35 vs 21%; OR, 2.73; 95% CI, 1.68 to 4.43; P value not reported).<br><br>Significant decreases in FPG were achieved with liraglutide compared to exenatide (-1.61 vs -0.60 mmol/L; treatment difference, -1.01 mmol/L; 95% CI, -1.37 to -0.65; P<0.0001).<br><br>In contrast, exenatide decreased PPG significantly more compared to liraglutide after breakfast (treatment difference, -1.33 mmol/L; 95% CI, 0.80 to 1.86; P<0.0001) and dinner (treatment difference, -1.01 mmol/L; 95% CI, 0.44 to 1.57; P=0.0005). After lunch differences between the two treatments were not significant (data not reported).<br><br>Both treatments were associated with decreases in body weight (-3.24 vs -2.87 kg; treatment difference, -0.37 kg; 95% CI, -0.99 to 0.23; P=0.2235). |

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| | | | | Increases in HOMA-B were significant with liraglutide compared to exenatide (32.12 vs 2.74%; treatment difference, 29.38%; 95% CI, 16.81 to 41.93; P<0.0001).<br><br>Decreases in fasting glucagon were not different between the two treatments (-19.44 vs -12.33 ng/L; treatment difference, -7.11 ng/L; 95% CI, -16.66 to 2.43; P=0.1436).<br><br>No differences were observed between the two treatments in terms of decreases in SBP (P=0.6409) or DBP (P=0.1610).<br><br>In terms of lipid profiles, significant changes favoring liraglutide were observed only for VLDL-C (P=0.0277), TG (P=0.0485), and FFA (P=0.0014). All other lipid parameters were similar between the two treatments. |
| Buse et al.[48] (2010)<br><br>Liraglutide 1.8 mg SC QD (continued liraglutide)<br><br>vs<br><br>liraglutide 1.8 mg SC QD (switched to liraglutide)<br><br>Patients enrolled in LEAD-6 who were randomized to exenatide 10 µg SC BID were transitioned to liraglutide 1.8 mg SC QD after the initial 26 week trial period. | ES (LEAD-6[47])<br><br>Type 2 diabetic patients 18 to 80 years of age with $HbA_{1c}$ 7.0 to 11.0%; BMI ≤45 kg/m$^2$; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months | N=376<br><br>14 weeks (40 weeks total) | Primary:<br>Change in baseline $HbA_{1c}$, FPG, body weight, and SBP; adverse events<br><br>Secondary:<br>Not reported | Primary:<br>$HbA_{1c}$ decreased further from 7.2% at week 26 to 6.9±0.32% at week 40 (P<0.0001) after switching from exenatide to liraglutide, but remained similar with continued liraglutide treatment (7.0 to 6.9±-0.06%; P=0.1222). Additional patients reached $HbA_{1c}$ targets after switching from exenatide to liraglutide.<br><br>After switching from exenatide to liraglutide, further decreases in FPG (-0.9±0.16 mmol/L; P<0.0001), body weight (-0.9±0.15 kg; P<0.0001), and SBP (-3.8±0.84 mmHg; P<0.0001) occurred, while HOMA-B increased (14.5±4.4%; P=0.001), consistent with FPG reductions. With continued liraglutide treatment, reductions in FPG (-0.2±0.11 mmol/L; P=0.0973), body weight (-0.4±0.15 kg; P=0.0089), and SBP (-2.2±0.88 mmHg; P=0.0128) occurred.<br><br>No significant changes in PPG occurred in either treatment group (P value not reported).<br><br>Similar numbers of patients reported one or more adverse events during the ES (37.6 vs 37.4%; P value not reported). Most adverse events were mild in severity. Nausea and diarrhea occurred in 1.5% of patients who continued liraglutide and 3.2% of patients who switched from exenatide to liraglutide, whereas vomiting occurred in 2.0% of patients who continued liraglutide and |

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| | | | | 0.5% of patients who switched from exenatide to liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide. Four patients who switched from exenatide to liraglutide had seven severe adverse events (cardiac failure, MI, cataract, chest discomfort, COPD, and dyspnea). Five patients continuing liraglutide had eight severe adverse events (cerebral infarction, cerebrovascular accident, TIA, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, and depression). Calcitonin levels remained at the lower level of the normal range (<1 pg/mL) and did not differ between treatment groups. No medullary thyroid carcinoma or pancreatitis cases were reported.<br><br>Secondary:<br>Not reported |
| Heine et al.[49] (2005)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID<br><br>vs<br><br>insulin glargine QD at bedtime<br><br>All patients were receiving existing metformin and/or sulfonylurea regimens. | OL, RCT<br><br>Patients 30 to 75 years of age with type 2 diabetes not adequately controlled (defined as $HbA_{1c}$ 7.0 to 10.0%) with combination metformin and sulfonylurea therapy at maximally effective doses, BMI 25 to 45 kg/m$^2$ and a history of stable body weight (≤10% variation for ≥3 months before screening) | N=551<br><br>26 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Change in FPG, fasting glucose <100 mg/dL and body weight loss | Primary:<br>At 26 weeks, similar reductions in $HbA_{1c}$ were noted between exenatide and insulin glargine (–1.11%, CI, –0.123 to 0.157).<br><br>Secondary:<br>A significantly reduction in FPG from baseline was observed in the insulin glargine group (–51.5 mg/dL; P<0.001). The reduction from baseline in the exenatide group was not significant (–25.7 mg/dL). A significant reduction was observed in the insulin group when compared to the exenatide group (95% CI, 20 to 34 mg/dL).<br><br>A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; P<0.001).<br><br>A significant weight loss was experienced in the exenatide group (–2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, –4.6 to –3.5 kg; P<0.001).<br><br>Similar rates of hypoglycemia were reported with both agents (CI, –1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of daytime hypoglycemia (CI, 0.4 to 4.9 events/patient-year), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, –2.3 to –0.9 events/patient-year). |

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| | | | | A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; P<0.001), vomiting (17.4 vs 3.7%; P<0.001) and diarrhea (8.5 vs 3%; P=0.006), upper abdominal pain (P=0.012), constipation (P=0.011), dyspepsia (P=0.011), decreased appetite (P=0.021), and anorexia (P=0.002) were reported in the exenatide group vs the insulin group.<br><br>Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients. |
| Secnik Boye et al.[50] (2006)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID<br><br>vs<br><br>insulin glargine QD at bedtime<br><br>All patients were receiving existing metformin and/or sulfonylurea regimens. | MC, OL, RCT<br><br>Secondary analysis on patients with type 2 diabetes inadequately controlled (defined as an $HbA_{1c}$ 7.0 to 10.0%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week study | N=455<br><br>26 weeks | Primary:<br>Patient-reported health outcome measures: Diabetes Symptom Checklist-revised, DTSQ, EQ-5D, Medical Outcomes Study 36-Item Short-Form Health Survey, Diabetes Treatment Flexibility Score<br><br>Secondary:<br>Not reported | Primary:<br>Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by Diabetes Symptom Checklist-revised overall scores, DTSQ, EQ-5D and Medical Outcomes Study 36-Item Short-Form Health Survey scores (P<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures (P>0.05 for all measures).<br><br>Neither the exenatide nor the insulin glargine group experienced a significant improvement in Treatment Flexibility Score scores (P=0.93 for both groups).<br><br>Secondary:<br>Not reported |
| Nauck et al.[51] (2007)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID vs<br><br>insulin aspart BID<br><br>All patients were receiving existing | MC, OL, RCT<br><br>Patients 30 to 75 years of age who had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, $HbA_{1c}$ | N=501<br><br>52 weeks | Primary:<br>Mean change in $HbA_{1c}$ levels, weight, fasting serum glucose levels, PPG levels, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>There was not a significantly different change from baseline in mean $HbA_{1c}$ levels between the exenatide (–1.04%) and insulin aspart groups (–0.89%, 95% CI, −0.32% to 0.01%; P=0.067).<br><br>Patients in the exenatide group experienced a gradual weight loss of –2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (95% CI, −5.9 to −5.0; P<0.001) at the end of 52 weeks.<br><br>Patients in both exenatide (–1.8 mmol/L) and insulin aspart (–1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (P<0.001 for both groups). There was not a significant difference |

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| metformin and/or sulfonylurea regimens. | levels ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m$^2$, and a history of stable body weight (≤10% variation for ≥3 months) | | | between groups (CI, −0.6 to 0.4; P=0.689).<br><br>Patients in the insulin aspart group had significantly lower mean glucose values at pre-breakfast (P=0.037), pre-lunch (P=0.004) and 03.00 hours (P=0.002). Patients in the exenatide group had a greater reduction in PPG excursions following morning (P<0.001), midday (P=0.002) and evening meals (P<0.001).<br><br>The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), diarrhea (9.5 vs 2%) and other clinically relevant adverse events (13.4 vs 6.4%).<br><br>Secondary:<br>Not reported |
| Diamant et al.[52] (2010)<br>DURATION-3<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>insulin glargine SC QD<br><br>All patients received existing background oral glucose-lowering regimens. | OL, PG, RCT<br><br>Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, $HbA_{1c}$ 7.1 to 11.0%, BMI 25 to 45 kg/m$^2$, and a stable body weight ≥3 months | N=456<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported QOL, safety | Primary:<br>Decreases in $HbA_{1c}$ were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, $HbA_{1c}$ was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; P=0.031).<br><br>Secondary:<br>Significantly greater proportions of exenatide ER-treated patients achieved $HbA_{1c}$ <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients.<br><br>Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; P=0.001).<br><br>With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (P<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (P=0.022) and before breakfast |

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| | | | | (P<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (P=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (P=0.001) and evening meals (P=0.033).<br><br>Seventy nine percent of patients receiving exenatide ER experienced both a decrease in $HbA_{1c}$ and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in $HbA_{1c}$ and increase in body weight.<br><br>Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; P<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed.<br><br>Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; P<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; P<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed.<br><br>Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported).<br><br>Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse |

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| | | | | events were reported by more than one patient, except chest pain (two patients). |
| Diamant et al.[53] (2012) DURATION-3<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>insulin glargine SC QD<br><br>All patients received existing background oral glucose-lowering regimens. | ES of DURATION-3[52]<br><br>Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, $HbA_{1c}$ 7.1 to 11.0%, BMI 25 to 45 kg/m$^2$, and a stable body weight ≥3 months | N=390<br><br>84 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportions of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety | Primary:<br>At 84 weeks, $HbA_{1c}$ decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (P=0.029).<br><br>Secondary:<br>The proportions of patients who achieved end point $HbA_{1c}$ targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (P=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (P=0.009), respectively.<br><br>Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (P<0.001).<br><br>Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001).<br><br>Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine. |
| Derosa et al.[54] (2011)<br><br>Exenatide 5 µg SC BID, titrated up to 10 µg SC BID<br><br>vs<br><br>glimepiride 1 mg TID, titrated up to 2 mg TID | MC, RCT, SB<br><br>Patients ≥18 years of age with type 2 diabetes intolerant to metformin at the highest dosages (2,500 to 3,000 mg/day) | N=111<br><br>12 months | Primary:<br>Change in baseline body weight, glycemic control, insulin resistance<br><br>Secondary:<br>Not reported | Primary:<br>There was decrease of body weight and BMI after six, nine, and 12 months (P<0.05, P<0.01, P<0.001, respectively) with exenatide, not obtained with glimepiride. BMI reached with exenatide was significantly lower compared to glimepiride (P<0.05).<br><br>A similar decrease in $HbA_{1c}$, FPG, and PPG after nine (P<0.05 for all), and after 12 months (P<0.01 for all) with both treatments, without significant differences between the two treatments.<br><br>Exenatide resulted in a reduction of fasting plasma insulin, and HOMA-IR after 12 months (P<0.05 for both), not observed with glimepiride; fasting plasma insulin increased with glimeperide. Values reached with exenatide were significantly lower compared to values reached with glimepiride after 12 months (P<0.05). |

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| | | | | Exenatide, but not glimepiride, gave an increase of adiponectin after 12 months (P<0.05), and the value registered with exenatide was significantly higher compared to the value recorded with glimepiride at trial end (P<0.05).<br><br>A decrease of tumor necrosis factor-α was observed after 12 months (P<0.05) with exenatide, but no with glimepiride; furthermore the value obtained with exenatide was significantly better compared to the value obtained with glimepiride after 12 months (P<0.05). Exenatide, but not glimepiride, gave a reduction of high sensitivity CRP after nine and 12 months (P<.0.05 and P<0.01) compared to baseline and glimepiride (P<0.05).<br><br>Secondary:<br>Not reported |
| Yang et al.[55] (2011)<br><br>Liraglutide 0.6, 1.2, or 1.8 mg QD<br><br>vs<br><br>glimepiride 4 mg QD<br><br>All patients received metformin. | AC, DB, DD, RCT<br><br>Adult patients with type 2 diabetes | N=929<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportions of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, body weight, BP, hypoglycemia, adverse events | Primary:<br>Baseline $HbA_{1c}$ was significantly reduced with all treatments. Treatment with liraglutide 1.2 and 1.8 mg was non-inferior to glimepiride (mean reduction: 1.36, 1.45, 1.39% points, respectively).<br><br>Secondary:<br>No significant difference was shown in the proportion of patients achieving $HbA_{1c}$ <7.0 or ≤6.5% between liraglutide 1.2 and 1.8 mg and glimepiride.<br><br>Liraglutide resulted in a mean reduction in weight of -1.8 to -2.4 kg compared to 0.1 kg weight gain with glimepiride.<br><br>Liraglutide significantly reduced SBP compared to glimepiride.<br><br>Two patients receiving glimeperide experienced major hypoglycemia compared to zero patients receiving liraglutide. Liraglutide was associated with a 10-fold lower incidence of minor hypoglycemia compared to glimeperide.<br><br>Gastrointestinal disorders were the most commonly reported adverse events with liraglutide therapy; events were transient and resulted in few withdrawals. |
| Bergenstal et al.[56] (2010) | DB, DD, MC, PG, RCT | N=514 | Primary:<br>Change in baseline | Primary:<br>Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased $HbA_{1c}$ |

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| DURATION-2<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>sitagliptin 100 mg QD<br><br>vs<br><br>pioglitazone 45 mg QD<br><br>All patients received existing metformin therapy. | Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, $HbA_{1c}$ 7.1 to 11.0%, and BMI 25 to 45 $kg/m^2$ | 26 weeks | $HbA_{1c}$<br><br>Secondary: Proportion of patients achieving an $HbA_{1c}$ ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported QOL, safety | compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165).<br><br>Secondary:<br>A significantly greater proportion of patients receiving exenatide achieved $HbA_{1c}$ targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone.<br><br>Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024).<br><br>In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported).<br><br>Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001).<br><br>Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).<br><br>Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001). |

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| | | | | Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only).<br><br>All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported).<br><br>All five domains of weight-related QOL and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406).<br><br>The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported. |
| Wyshman et al.[57] (2011)<br>DURATION-2<br><br>Exenatide ER 2 mg SC once weekly (continued exenatide ER)<br><br>vs | ES (DURATION-2[56])<br><br>Type 2 diabetics ≥18 years of age, receiving stable metformin therapy for ≥2 months, $HbA_{1c}$ 7.1 to 11.0%, and BMI 25 to 45 | N=319<br><br>26 weeks (52 weeks total) | Primary:<br>Change in baseline $HbA_{1c}$, FPG, body weight, proportion of patients achieving an $HbA_{1c}$ <7.0 or ≤6.5%, proportion of patients achieving FPG <7 | Primary:<br>Patients who continued exenatide ER demonstrated significant 52 week improvements in $HbA_{1c}$ (-1.6±0.1%), FPG (-1.8±0.3 mmol/L), and body weight (-1.8±0.5 kg; P=0.0002 vs baseline). Patients originally receiving sitagliptin who switched to exenatide ER demonstrated significant incremental improvements in $HbA_{1c}$ (-0.3±0.1%; P=0.0010), FPG (-0.7±0.2 mmol/L; P=0.0017), and body weight (-1.1±0.3 kg; P=0.0006). Patients originally receiving pioglitazone who switched to exenatide ER maintained $HbA_{1c}$ and FPG improvements (week 52, -1.6±0.1% and -1.7±0.3 mmol/L, with significant weight loss; -3.0±0.3 kg; P<0.0001). |

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| exenatide ER 2 mg SC once weekly (switched to exenatide ER)<br><br>Patients enrolled in DURATION-2 who were randomized to sitagliptin 100 mg QD or pioglitazone 45 mg QD were transitioned to exenatide ER 2 mg SC once weekly after the initial 26 week trial period. | $kg/m^2$ | | mmol/L, and markers of cardiovascular risk at week 52 and from week 26 to 52; safety<br><br>Secondary:<br>Not reported | No differences in the proportions of patients achieving target $HbA_{1c}$ <7.0 or ≤6.5% were observed between weeks 26 and 52 in patients who continued exenatide ER and who switched to exenatide ER from pioglitazone. A significantly greater proportion of patients achieved both targets after switching from sitagliptin to exenatide ER (P<0.05 for both). Similar results were observed for the FPG target (<7 mmol/L) (P=0.0002).<br><br>Patients who continued exenatide ER achieved greater SBP improvements at week 52 (-12.2 mm Hg; 95% CI, -16.1 to -8.3). Patients with abnormal SBP at 26 weeks who were receiving sitagliptin and pioglitazone, achieved greater SBP decreases (-11.3 [95% CI, -14.9 to -7.7] and -9.4 mm Hg [95% CI, -13.4 to -5.3], respectively) at week 52. Patients who continued exenatide ER maintained improvements in HDL-C at week 52; all other lipid variables were not different from baseline. Patients switched to exenatide ER from sitagliptin maintained HDL-C improvements and achieved a significant decrease in TC at week 52. Patients switched to exenatide ER from pioglitazone achieved significant decreases in HDL-C, LDL-C, and TC at week 52. Patients who continued exenatide ER achieved improvements in urinary albumin/creatinine ratio, BNP, and high-sensitivity CRP. The urinary albumin/creatinine ratio was significantly decreased for all treatment groups by week 52. Patients who switched to exenatide ER from sitagliptin and pioglitazone achieved significant reductions in BNP, with high-sensitivity CRP and plasminogen activator inhibitor-1 improvements observed after 26 weeks of initial treatment with pioglitazone were not maintained once switched to exenatide ER.<br><br>Exenatide ER was well tolerated and adverse events were predominantly mild or moderate in intensity. Nausea was the most frequent adverse event (continued exenatide ER, 5%; switched to exenatide ER from sitagliptin, 11%; switched to exenatide ER from pioglitazone, 10%). No major cases of hypoglycemia or pancreatitis were reported.<br><br>Secondary:<br>Not reported |
| Garber et al.[58] (2009)<br>LEAD-3 | AC, DB, DD, MC, PG, RCT | N=746<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>Decreases in $HbA_{1c}$ were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with |

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| Liraglutide 1.2 and 1.8 mg SC QD<br><br>vs<br><br>glimepiride 8 mg/day | Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and $HbA_{1c}$ 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy) | | Secondary:<br>Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported QOL | liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; P<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; P=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; P=0.0046).<br><br>Secondary:<br>Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (P values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks.<br><br>Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; P=0.027 and 1.8 mg, -1.42 mmol/L; P=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L).<br><br>Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs glimepiride; P=0.1616, liraglutide 1.8 mg vs glimepiride; P=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; P=0.1319).<br><br>Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (P=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (P<0.0118). Mean DBP decreased but not significantly with any treatment.<br><br>HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (P=0.0249 and P=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride).<br><br>Patients receiving liraglutide 1.8 mg reported improved QOL scoring for physical and emotional domains compared to glimepiride (P=0.02). Improvements were largely as a result of improvements in weight image and weight concern (P<0.01). |
| Garber et al.[59] (2011)<br>LEAD-3 | ES (LEAD-3[58])<br><br>Type 2 diabetic | N=440<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>The decrease in $HbA_{1c}$ was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; P=0.0376) and 1.8 mg (-1.1 vs -0.6%; P=0.0016) compared to |

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| Liraglutide 1.2 mg and 1.8 mg SC QD<br><br>vs<br><br>glimepiride 8 mg/day | patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and $HbA_{1c}$ 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy) | | Secondary:<br>Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP | glimepiride over two years of treatment.<br><br>Secondary:<br>Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; P<0.001 for both comparisons).<br><br>Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (P=0.0015 and P=0.0001, respectively).<br><br>In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (P=0.0451 for liraglutide 1.2 mg vs glimepiride).<br><br>The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (P values not reported).<br><br>After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (P values not reported).<br><br>No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment. |
| Bode et al.[60] (2010)<br>LEAD-3<br><br>Liraglutide 1.2 and 1.8 mg SC QD<br><br>vs<br><br>glimepiride 8 mg/day | Post-hoc analysis (LEAD-3[58])<br><br>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent | N=746<br><br>52 weeks | Primary:<br>Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive | Primary:<br>Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point "my weight is just right" was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (P=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; P<0.0001 and liraglutide 1.8 mg; P<0.001).<br><br>Logistic regression estimates indicated that patients receiving liraglutide 1.8 |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months and $HbA_{1c}$ 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy) | | functioning and health<br><br>Secondary:<br>Not reported | mg were 52% less likely to report feeling either "somewhat" or "very overweight" vs "just right", "somewhat underweight," or "very overweight" during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; P value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being "somewhat worried", "very worried," or "extremely worried" vs "a little concerned" or "not concerned at all" about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; P value not reported).<br><br>There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any of the cognitive functioning and performance scales during treatment (P values not reported).<br><br>The health-related QOL composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (P=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (P<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (P values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (P=0.006).<br><br>Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (P<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses.<br><br>Decreases in $HbA_{1c}$ corresponded to improvements in general perceived health (P<0.0001), cognitive functioning composite score (P=0.006), and cognitive performance (P=0.004). Correlations of change in $HbA_{1c}$ within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Not reported |
| Amori et al.[61] (2007)<br><br>Incretin therapy (exenatide, liraglutide*, sitagliptin and vildagliptin*)<br><br>vs<br><br>non-incretin-based therapy (placebo or hypoglycemic agent) | MA (29 RCTs)<br><br>Type 2 diabetics | N=12,996<br><br>Duration varied (12 to 52 weeks) | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, proportion of patients achieving an $HbA_{1c}$ <7.0% | Primary:<br>Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in $HbA_{1c}$ favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81).<br><br>Specifically, no difference in the $HbA_{1c}$ was found in OL non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar $HbA_{1c}$ efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported).<br><br>Secondary:<br>Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21).<br><br>Exenatide-treated patients were more likely to achieve an $HbA_{1c}$ <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported. |
| Pinelli et al.[62] (2008)<br><br>Exenatide in combination with other antidiabetic agents<br><br>vs<br><br>TZD in combination with other antidiabetic agents | MA (22 RCTs)<br><br>Patients with type 2 diabetes receiving combination therapy | N=9,325<br><br>≥24 weeks | Primary:<br>Mean change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients reaching $HbA_{1c}$ <7.0%, mean change from baseline in FPG and body weight, hypoglycemia, gastrointestinal adverse events | Primary:<br>There were small reductions in $HbA_{1c}$ across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide.<br><br>When only PC trials were analyzed, there were greater reductions in $HbA_{1c}$ with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83).<br><br>When only TZD AC trials were analyzed, there was a significant difference in $HbA_{1c}$ levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01).<br><br>There was no difference in $HbA_{1c}$ reduction between exenatide and insulin comparators in OL, NI trials.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | TZD and exenatide-based therapies were associated with OR of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching $HbA_{1c}$ <7.0%.<br><br>FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31).<br><br>Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32).<br><br>In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64).<br><br>The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and 4% in patients receiving comparator. |

*Agent is not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, XL=extended-release
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, ES=extension study, IA=interim analysis, MC=multicenter, NI=noninferiority, OE=open-ended, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, RETRO=retrospective, SB=single-blind, SR=systematic review, TB=triple-blind, XO=cross-over
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo B=apolipoprotein B, AST=aspartate aminotransferase, AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, COPD=chronic obstructive pulmonary disease, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, $HbA_{1c}$=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, LSM=least squares mean, MI=myocardial infarction, PAI-1=plasminogen activator inhibitor-1, OR=odds ratio, PPG=post-prandial glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TZD=thiazolidinedione, VLDL-C=very low density lipoprotein cholesterol, WMD=weighted mean difference

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 10. Relative Cost of the Incretin Mimetics**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Exenatide | injection | Byetta®, Bydureon® | $$$$$ | N/A |
| Liraglutide | injection | Victoza® | $$$$$ | N/A |

N/A=Not available

## X. Conclusions

The incretin mimetics are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[4] Currently, exenatide and liraglutide are the only incretin mimetics available. There are no generic products in this class.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high $HbA_{1c}$ will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The incretin mimetics are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, an established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. Patients who are not appropriate for initial therapy with metformin, may be initiated on

another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DDP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one incretin mimetic over another is not stated.[6-15]

A variety of clinical trials have been conducted evaluating the incretin mimetics. The incretin mimetics have been evaluated in combination with and in comparison to a variety of antidiabetic therapies. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens. Overall, the incretin mimetics are effective in improving glycosylated hemoglobin ($HbA_{1c}$), fasting plasma glucose, post-prandial glucose, and body weight. Efficacy data comparing the incretin mimetics to other antidiabetic agents are not consistent, with the incretin mimetics achieving significantly greater or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents. A limited number of head-to-head clinical trials have been conducted within the class. Results from these trials do not consistently demonstrate that one incretin mimetic is more effective than another.[17-62]

Gastrointestinal-related adverse events are common with incretin mimetics.[1-3] There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking exenatide.[4] There have also been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation.[4] Patients may develop antibodies to exenatide consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals.[1,2]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with exenatide or any other antidiabetic drug.[1-3]

There is insufficient evidence to support that one brand incretin mimetic is safer or more efficacious than another within its given indication. Since the incretin mimetics are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, they should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand incretin mimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Insulins
# AHFS Class 682008
# November 14, 2012

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Insulins stimulate peripheral glucose uptake by skeletal muscle and fat, decrease hepatic glucose production, inhibit lipolysis and proteolysis, and enhance protein synthesis.[1-17]There are two types of insulin preparations currently available: human insulin and insulin analogs. Human insulin is derived from a biosynthetic process and is structurally identical to endogenous insulin. Insulin analogs are structurally different than human insulin. Each insulin analog differs in the addition, deletion, or substitution of amino acids on the B chain. These modifications lead to a faster onset and shorter duration of action (for rapid-acting insulin analogs) or slower absorption and a longer duration of action (for long-acting insulin analogs) than human insulins.[1,2]

The insulin preparations are further categorized based on their duration of action. Rapid- and short-acting insulins are administered as a bolus prior to meals to control postprandial glucose excursions. They may also be administered continuously via an infusion pump. Intermediate- and long-acting insulins are administered once or twice daily. They act as basal insulin to decrease hepatic glucose production and lower fasting plasma glucose concentrations.[1,2]

The insulins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic formulations of insulin; however, there are several products available over-the-counter. This class was last reviewed in May 2010.

**Table 1. Insulins Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| **Rapid-Acting Insulins** | | | |
| Insulin aspart | injection | NovoLog® | none |
| Insulin glulisine | injection | Apidra®, Apidra Solostar® | none |
| Insulin lispro | injection | Humalog® | Humalog® |
| **Short-Acting Insulins** | | | |
| Insulin regular, human | injection | Humulin®‡ R, Novolin®‡ R | Humulin®‡ R, Novolin®‡ R |
| **Intermediate-Acting Insulins** | | | |
| NPH, human insulin isophane | injection | Humulin®‡ N, Novolin®‡ N | Humulin®‡ N, Novolin®‡ N |
| **Long-Acting Insulins** | | | |
| Insulin detemir | injection | Levemir® | none |
| Insulin glargine, human recombinant analog | injection | Lantus®, Lantus Solostar® | Lantus® |
| **Combination Insulins (Intermediate-Acting and Rapid-Acting)** | | | |
| Insulin aspart protamine and insulin aspart | injection | NovoLog® Mix 70/30 | none |
| Insulin lispro protamine and insulin lispro | injection | Humalog® Mix 50/50, Humalog® Mix 75/25 | none |
| **Combination Insulins (Intermediate-Acting and Short-Acting)** | | | |
| NPH, human insulin isophane and insulin regular, human | injection | Humulin®‡ 70/30, Novolin®‡ 70/30 | Humulin®‡ 70/30, Novolin®‡ 70/30 |

‡Product is available over-the-counter.
PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Insulins**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association: **Standards of Medical Care in Diabetes[18] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes<br>• An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 1 diabetes<br>• Recommended therapy consists of the following components:<br>  ○ Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy.<br>  ○ Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity.<br>  ○ For many patients, use of insulin analogs.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/ European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[19] (2012)** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy.<br><br>Initial drug therapy<br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br>Advancing to dual combination therapy<br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over |

| Clinical Guideline | Recommendation(s) |
|---|---|

approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.

- On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.
- If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.
- Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
- It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.
- For all medications, consideration should also be given to overall tolerability.

Advancing to triple combination therapy

- Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
- Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
- In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
- Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

**Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations**

| **Initial Drug Monotherapy** | Metformin | | | | |
|---|---|---|---|---|---|
| Efficacy (↓$HbA_{1c}$) | High | | | | |
| Hypoglycemia | Low risk | | | | |
| Weight | Neutral/loss | | | | |
| Side Effects | Gastrointestinal/lactic acidosis | | | | |
| If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference) | | | | | |
| **Two Drug Combin-ations** | Metformin + sulfonyl-urea | Metformin + thia-zolidinedione (TZD) | Metformin + DPP-4 inhibitor | Metformin + GLP-1 receptor agonist | Metformin + insulin (usually basal) |
| Efficacy (↓$HbA_{1c}$) | High | High | Inter-mediate | High | Highest |
| Hypo-glycemia | Moderate risk | Low risk | Low risk | Low risk | High risk |
| Weight | Gain | Gain | Neutral | Loss | Gain |
| Major Side Effects | Hypo-glycemia | Oedema, heart failure, bone fracture | Rare | Gastro-intestinal | Hypo-glycemia |
| If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference) | | | | | |
| **Three Drug Combin-ations** | Metformin + sulfonyl-urea + | Metformin + TZD + | Metformin + DPP-4 inhibitor + | Metformin + GLP-1 receptor agonist | Metformin + insulin therapy + |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | <table><tr><td></td><td>TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>+<br>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr><tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr><tr><td colspan="2">More Complex Insulin Strategies</td><td colspan="4">Insulin (multiple daily doses)</td></tr></table> |
| American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[20] (2012)** | • Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.<br>• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.<br>• It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. |
| American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[21] (2011)** | Antihyperglycemic pharmacotherapy<br>• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[11]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus:<br>**Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[22] (2009)** | <u>Principles underlying the algorithm</u><br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action.<br>• Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br><u>Stratification by current $HbA_{1c}$</u><br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br><u>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%</u><br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated.<br>• The following triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + GLP-1 receptor agonist + glinide.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>  ○ Metformin + DPP-4 inhibitor + glinide.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist.<br>  ○ Metformin + DPP-4 inhibitor.<br>  ○ Metformin + TZD.<br>  ○ Metformin + sulfonylurea. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | ○ Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>○ Metformin + GLP-1 receptor agonist + TZD.<br>○ Metformin + DPP-4 inhibitor + TZD.<br>○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>○ Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>○ Metformin + GLP-1 receptor agonist.<br>○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>○ Metformin + DPP-4 inhibitor.<br>○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>○ Metformin + TZD. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | ○ Metformin + TZD + sulfonylurea.<br>○ Metformin + GLP-1 receptor agonist + TZD.<br>○ Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy.<br><br><u>General considerations regarding insulin therapy</u><br>• Therapy can be initiated with basal, premixed, prandial, or basal-bolus insulin.<br>• Long-acting basal insulin is generally the initial choice for initiation of insulin therapy. Insulin glargine and insulin detemir are preferred over human NPH insulin because they have relatively peakless time-action curves and a more consistent effect from day to day, resulting in a lower risk of hypoglycemia.<br>• If the patient has failed to achieve goals with the use of basal insulin, an alternative approach would be to use premixed insulin analogs (lispro-protamine or aspart-protamine) with 2 injections per day. The patient must have a fairly constant lifestyle with use of premixed insulin and may have a higher risk of hypoglycemia.<br>• A basal-bolus insulin regimen with four injections per day is usually more efficacious and provides greater flexibility for patients.<br>• Metformin is the most commonly used and safest medication to combine with insulin.<br>• Exenatide and DPP-4 inhibitors have not been approved by the FDA for concomitant use with insulin. |

| Clinical Guideline | Recommendation(s) |
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| | • Colesevelam and alpha-glucosidase inhibitors are unlikely to contribute to effectiveness of insulin.<br>• Sulfonylureas and glinides should be discontinued when prandial insulin is started because postprandial glucose can be managed better with a rapid-acting insulin analogue or a premixed insulin preparation.<br>• TZDs in combination with insulin have been associated with weight gain, fluid retention, congestive heart failure, and increased risk of fractures. Recent clinical trials (ADVANCE, VADT, and ACCORD) showed no increased risk of mortality associated with rosiglitazone. The PROACTIVE trial showed a small beneficial effect of pioglitazone on cardiac events. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[23] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>• Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>• Initiate self-monitoring blood glucose levels.<br><br><u>Glycemic management-patients with type 1 diabetes</u><br>• Initiate intensive insulin therapy with one of the following regimens:<br>  ○ Basal-bolus therapy, using a long-acting insulin analog in combination with a rapid-acting insulin analog or inhaled insulin at meals.<br>  ○ Continuous SC insulin infusion with an insulin pump; insulin pump therapy indicated for:<br>  ▪ Patients unable to achieve control using a regimen of multiple daily injections.<br>  ▪ Patients with histories of frequent hypoglycemia and/or hypoglycemia unawareness.<br>  ▪ Patients who are pregnant.<br>  ▪ Patients with extreme insulin sensitivity (pump therapy facilitates better precision than SC injections).<br>  ▪ Patients with a history of dawn phenomenon (these patients can program a higher basal rate for the early morning hours to counteract the rise in blood glucose concentration).<br>  ▪ Patients who require more intensive diabetes management because of complications including neuropathy, nephropathy, and retinopathy.<br>  ▪ Patients taking multiple daily injections who have demonstrated willingness and ability to comply with prescribed diabetes self-care behavior including frequent glucose monitoring, carbohydrate counting, and insulin adjustment.<br>• Consider adding pramlintide to intensive insulin therapy to enhance glycemic control and to assist with weight management.<br>• Consider adding an insulin sensitizer to address insulin resistance as needed. Exercise caution because of the potential for increased fluid retention when TZDs are used with insulin.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor |

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| | glucose levels at least three times daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>  ○ First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>  ○ After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>  ○ If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>  ○ Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>  ○ Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>  ○ Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>  ○ Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times |

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| | daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 1 diabetes</u><br>• Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range.<br>• Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated.<br>• Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients.<br>• Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability.<br>• Carefully assess PPG levels when the $HbA_{1c}$ level is elevated and pre-meal glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable $HbA_{1c}$ level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia.<br>• Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs.<br>• Individualize insulin regimens to accommodate patient exercise patterns.<br>• Treat hypoglycemic reactions with simple carbohydrates.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or |

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| | intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[24] (2009)** | <u>DPP-4 inhibitors</u><br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in 6 months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br><u>TZDs</u><br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate |

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| | ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  o A body mass index ≥35 $kg/m^2$ in those of European descent (with appropriate adjustment for other ethnic groups).<br>  o A BMI <35 $kg/m^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  o A person prefers injecting insulin immediately before a meal.<br>  o Hypoglycemia is a problem.<br>  o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>  o Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>  o Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>  o Who cannot use the device needed to inject NPH insulin but |

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| | who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>o Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[25] (2008)** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br><u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>o The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>o A sulfonylurea if metformin is not tolerated.<br>o Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br><u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u> |

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| | • Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/m$^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  o Inadequate blood glucose control ($HbA_{1c}$ ≥7.5%) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  o Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started.<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in 6 months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  o Continue with metformin and the sulfonylurea (and acarbose, if used).<br>  o Review the use of the sulfonylurea if hypoglycemia occurs.<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>  o Continue with metformin.<br>  o Continue the sulfonylurea initially and discontinue if hypoglycemia occurs.<br>• Consider combining pioglitazone with insulin therapy for:<br>  o Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>  o Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>  o Those who require assistance from a care taker or healthcare professional to administer their insulin injections.<br>  o Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes.<br>  o Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ >9.0 %. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>  o Immediate injection before a meal is preferred. |

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| | ○ Hypoglycemia is a problem.<br>○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[26] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required.<br><br>Insulin as an adjunct to oral therapy<br>• A once-daily dose of NPH, detemir or glargine insulin is added to metformin or TZDs. If patient is also on a sulfonylurea, it may be discontinued or reduced when insulin is added.<br>• A once-daily dose of insulin is added to sulfonylurea. Glargine or detemir may be dosed in the morning or evening. Morning dosing may prevent nighttime hypoglycemic episodes and may also provide for improved blood glucose control.<br><br>Insulin alone<br>• Twice-daily insulin regimen is established with progression to increased frequency of insulin administration as necessary to achieve treatment goals or to add flexibility to a patient's meal and activity schedules.<br>• Multiple dose insulin with rapid-acting and basal insulin therapy may offer patients with active lifestyles the greatest flexibility.<br><br>Oral agents as an adjunct to insulin therapy<br>• Metformin may be a useful adjunct for patients who require large doses of insulin (>100 units/day). |
| International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes[27] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is |

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| | contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br><u>Insulin</u><br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |
| American Diabetes Association (ADA):<br>**Care of Children and Adolescents with Type 1 Diabetes[28] (2005)** | • Insulin type, mixture of insulins, site of injection, and individual patient response differences can all affect the onset, peak, and duration of insulin activity.<br>• Children with diabetes often require multiple daily injections of insulin, using combinations of rapid-, short-, intermediate-, or long-acting insulin before meals and at bedtime to maintain optimal blood glucose control.<br>• The basal/bolus insulin regimen uses a long-acting insulin analog combined with a rapid-acting insulin analog given before meals and snacks. This regimen has been shown to result in stable glycemic control and less hypoglycemia compared with regimens using intermediate and short insulin regimens.<br>• Many young children and teenagers consume multiple snacks throughout the day. An ideal basal/bolus regimen may consist of as many as six to seven insulin injections per day. A combination of rapid-acting insulin with small amounts of intermediate-acting insulin to allow coverage for snacks may be an appropriate alternative to the basal/bolus plan. However, two or three doses of mixed rapid-acting or short-acting insulin with intermediate-acting insulin generally cannot maintain $HbA_{1c}$ levels within the target range. Recommendations now support moving toward a basal/bolus insulin regimen for most patients.<br>• The combination of rapid-acting insulin analogs and a long-acting insulin offers an excellent option for basal and bolus insulin administration.<br>• Basal/bolus regimens have been shown to result in lower fasting blood glucose levels with less nocturnal hypoglycemia than regimens that use NPH insulin in children/adolescents, as well as in adults. |
| National Institute for Clinical Excellence:<br>**Managing Type 1 Diabetes in Adults (full guideline part 2)[29] (2008)** | <u>Insulin regimens</u><br>• Patients should have access to the types (preparation and species) of insulin they find allow them optimal well-being.<br>• Cultural preferences need to be discussed and respected in agreeing on the insulin regimen for a patient.<br>• Multiple insulin injection regimens, in patients who prefer them, should be used as part of an integrated package of which education, food, and skills training should be integral parts.<br>• Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes.<br>• Mealtime insulin injections should be provided by injection unmodified ('soluble') insulin or rapid-acting insulin analogs before main meals.<br>• Rapid-acting insulin analogs should be used as an alternative to |

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| | mealtime unmodified insulin where nocturnal or late inter-prandial hypoglycemia is a problem, and in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired.<br>• Basal insulin therapy (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogs (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogs are given at mealtimes or the midday insulin dose is small or lacking, the need to give isophane (NPH) insulin twice-daily (or more often) should be considered.<br>• Long-acting insulin analogs (insulin glargine) should be used when:<br>  ○ Nocturnal hypoglycemia is a problem on isophane (NPH) insulin.<br>  ○ Morning hypoglycemia on isophane (NPH) insulin results in difficult daytime blood glucose control.<br>  ○ Rapid-acting insulin analogues are used for mealtime blood glucose control.<br>• Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life:<br>  ○ Biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance.<br>  ○ Biphasic rapid-acting insulin analog pre-mixes may give an advantage to those prone to hypoglycemia at night.<br>  ○ Such twice-daily regimens may also help:<br>  ▪ Those who find adherence to their agreed lunchtime insulin injection difficult.<br>  ▪ Those with learning difficulties who may require assistance from others.<br>• Patients whose nutritional and physical activity patterns vary considerably from day-to-day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations and consideration of unusual patterns and combinations.<br>• For patients undergoing periods of fasting or sleep following eating (e.g., during religious feasts and fasts, after night-shift work), a rapid-acting insulin analog before the meal (provided the meal is not prolonged) should be considered.<br>• For patient with erratic and unpredictable blood glucose control, rather than a change in a previously optimized insulin regimen, the following should be considered:<br>  ○ Re-suspension of insulin and injection technique.<br>  ○ Injection sites.<br>  ○ Self-monitoring skills.<br>  ○ Knowledge and self-management skills.<br>  ○ Nature of lifestyle.<br>  ○ Psychological and psychosocial difficulties.<br>  ○ Possible organic causes (e.g., gastroparesis).<br>• Continuous SC insulin infusion is recommended as an option provided that:<br>  ○ Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and<br>  ○ Patients receiving the treatment have the commitment and competence to use the therapy effectively.<br>• Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some mealtime insulin) should be |

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| | considered for patients initiating insulin therapy, until such time as islet β-cell deficiency progresses further.<br>• Clear guidelines and protocols should be given to all patients to assist them in adjusting insulin doses appropriate during intercurrent illness.<br>• Oral glucose-lowering drugs should generally not be used in the management of type 1 diabetics.<br><br>Insulin delivery<br>• Patients who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen.<br>• Patients who have special visual or psychological needs should be provided with injection devices or needle-free systems that they can use independently for accurate dosing.<br>• Insulin injection should be made into the deep SC fat. To achieve this, needles of a length appropriate to the individual should be made available.<br>• Patients should be informed that the abdominal wall is the therapeutic choice for mealtime insulin injections.<br>• Patients should be informed that extended-acting suspension insulin (e.g., isophane [NPH] insulin) may give a longer profile of action when injected into the SC tissue of the thigh rather than the arm or abdominal wall.<br>• Patients should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within that area.<br>• Patients should be provided with suitable containers for the collection of used needles. Arrangements should be available for the suitable disposal of these containers.<br>• Injection site condition should be checked annually, and if new problems with blood glucose control occur. |
| National Institute for Clinical Excellence/National Collaborating Center for Women's and Children's Health: **Diagnosis and Management of Type 1 Diabetes in Children and Young People[30] (2004 and 2009 Update)** | Insulin regimens<br>• Pre-school and primary school children should be offered the most appropriate individualized regimens to optimize glycemic control.<br>• Young people should be offered multiple daily injection regimens to help optimize glycemia control.<br>• As it improves glycemic control, multiple daily injection regimens should be offered only as part of a package of care that involves continuing education; dietary management; instruction on the use of insulin delivery systems and blood glucose monitoring; emotional and behavioral support; and medical, nursing, and dietetic expertise in pediatric diabetes.<br>• Children and young people using multiple daily injection regimens should be informed that they may experience an initial increase in the risk of hypoglycemia and short-term weight gain.<br>• Children and young people and their families should be informed about strategies for the avoidance and management of hypoglycemia.<br>• Young people who do not achieve satisfactory glycemic control with multiple daily injection regimens should be offered additional support and, if appropriate, alternative insulin therapy (once, twice, or three times daily mixed insulin regimens or continuous SC insulin infusion using an insulin pump).<br>• Young people who have difficulty adhering to the multiple daily injection regimens should be offered twice-daily injection regimens.<br>• Continuous SC insulin infusion is recommended as an option for |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | patients provided that:<br>○ Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and;<br>○ Patients receiving the treatment have the commitment and competence to use the therapy effectively.<br>• Continuous SC insulin infusion therapy should be initiated only by a trained specialist team.<br>• All individuals beginning continuous SC insulin infusion therapy should be provided with specific training in its use.<br>• Established users of continuous SC insulin infusion therapy should have their insulin management reviewed by their specialist team so that a decision can be made about whether a trial or a switch to multiple-dose insulin incorporating insulin glargine would be appropriate.<br><br><u>Insulin preparations</u><br>• Children and young people should be offered the most appropriate insulin preparations according to their individual needs with the aim of obtaining an $HbA_{1c}$ <7.5% without frequent disabling hypoglycemia and maximizing quality of life.<br>• Children and young people using multiple daily insulin regimens should be informed that injection of rapid-acting insulin analogs before eating (rather than after eating) reduces PPG levels thus helps to optimize blood glucose control.<br>• For pre-school children it may be appropriate to use rapid-acting insulin analogs shortly after eating (rather than before eating) because food intake can be unpredictable.<br>• Children and young people who use insulin preparations containing intermediate-acting insulin should be informed that these preparations should be mixed before use according to instructions provided in patient information leaflets.<br><br><u>Insulin delivery</u><br>• Children and young people should be offered a choice of insulin delivery systems that takes account of their insulin requirements and personal preferences.<br>• Children and young people using insulin injection regimens should be offered needles that are of an appropriate length for their body fat.<br><br><u>Non-insulin agents (oral antidiabetic agents)</u><br>• Children and young people should not be offered acarbose or sulfonylureas in combination with insulin because they may increase the risk of hypoglycemia without improving glycemic control.<br>○ Metformin in combination with insulin is suitable for use only within research trials because the effectiveness of this combination therapy in providing glycemic control is uncertain. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the insulins are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Insulins[2-9]**

| Indication | Rapid-Acting Insulins | | | Short-Acting Insulins | Intermediate-Acting Insulins |
|---|---|---|---|---|---|
| | Insulin Aspart | Insulin Glulisine | Insulin Lispro | Insulin Regular, Human | NPH, Human Insulin Isophane |
| Adjunct to diet and exercise to improve glycemic control in adults and children with diabetes | | | | ✔ (Humulin® R) | |
| Diabetes | | | | | ✔ |
| Improve glycemic control in adults and children with diabetes mellitus | ✔ | ✔ | ✔ | ✔ (Novolin® R) | |
| Treatment of diabetic patients with marked insulin resistance (daily requirements more than 200 units), since a large dose may be administered subcutaneously in a reasonable volume | | | | ✔ * | |
| Other | | | | | ✔ † |

*Humulin® R (U 500)
†Humulin® N and Novolin® N are also approved for use with gestational diabetes, immunologic insulin resistance, injection-site lipodystrophy, local insulin allergy, and temporary use (e.g., acute stress, surgery).

**Table 4. FDA-Approved Indications for the Insulins (Continued)[2,10-17]**

| Indication | Long-Acting Insulins | | Combination Insulins (Intermediate-Acting and Rapid-Acting) | | Combination Insulins (Intermediate-Acting and Short-Acting) |
|---|---|---|---|---|---|
| | Insulin Detemir | Insulin Glargine, Human Recombinant Analog | Insulin Aspart Protamine/ Insulin Aspart | Insulin Lispro Protamine/ Insulin Lispro | NPH, Human Insulin Isophane/ Insulin Regular, Human |
| Diabetes | | | | | ✔ |
| Gestation diabetes | | | | | ✔ |
| Improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus | ✔ | ✔ | | | |
| Improve glycemic control in patients with diabetes mellitus | | | ✔ | | |
| Treatment of patients with diabetes for the control of hyperglycemia | | | | ✔ | |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the insulins are listed in Table 5.

**Table 5. Pharmacokinetic Parameters of the Insulins[1,2]**

| Generic Name(s) | Onset (hours) | Peak (hours) | Duration (hours) | Half-Life (hours) | Mixing of Insulins |
|---|---|---|---|---|---|
| **Rapid-Acting Insulins** | | | | | |
| Insulin aspart | 0.25 | 0.75 to 1.50 | 3 to 5 | 1.35 | NPH |
| Insulin glulisine | 0.33 | Not reported | 5.3 | 0.7 | NPH |
| Insulin lispro | Not reported | 0.5 to 1.5 | 3 to 4 | 0.43 to 0.87 | May be mixed with longer-acting insulin |
| **Short-Acting Insulins** | | | | | |
| Insulin regular, human | 0.5 to 2.5 | 2 to 15 | 8 to 22 | 1.4 to 3.3 | May be mixed with longer-acting insulin |
| **Intermediate-Acting Insulins** | | | | | |
| NPH, human insulin isophane | 0.5 to 1.5 | 2 to 12 | 24 | Not reported | Insulin regular, human |
| **Long-Acting Insulins** | | | | | |
| Insulin detemir | 3-4 | 6-8 | 5.7 to 23.2 | 5 to 7 | None |
| Insulin glargine, human recombinant analog | 1.1 | 5 | 10.8-24 | Not reported | None |
| **Combination Insulins (Intermediate-Acting and Rapid-Acting)** | | | | | |
| Insulin aspart protamine and insulin aspart | Not reported | Not reported | Not reported | Not reported | None |
| Insulin lispro protamine and insulin lispro | Not reported | Not reported | Not reported | Not reported | None |
| **Combination Insulins (Intermediate-Acting and Short-Acting)** | | | | | |
| NPH, human insulin isophane and insulin regular, human | Not reported | Not reported | Not reported | Not reported | None |

## V. Drug Interactions

Significant drug interactions with the insulins are listed in Table 6.

**Table 6. Significant Drug Interactions with the Insulins[2]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Insulin | 2 | β-Adrenergic blocking agents (β-blockers), nonselective | β-blockers may blunt the sympathetic mediated response to hypoglycemia and may mask hypoglycemic symptoms. Discontinue nonselective β-blocker therapy or switch to a β-blocker with selective activity if possible. |
| Insulin | 2 | Fenfluramine | Fenfluramine may potentiate the hypoglycemic effects of insulin. Monitor blood glucose concentrations and adjust dose of insulin as needed to avoid hypoglycemia. |
| Insulin | 2 | Monoamine oxidase inhibitors (MAOIs) | MAOIs may potentiate the hypoglycemic effects of insulin by stimulating insulin secretion and inhibiting gluconeogenesis. |

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| | | | Monitor blood glucose concentrations and adjust the dose of insulin as needed. |
| Insulin | 2 | Salicylates | Salicylates increase basal insulin secretion and acute insulin response to a glucose load. The hypoglycemic effects of insulin may be potentiated. Monitor blood glucose concentrations and adjust the dose of insulin as needed. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

Adverse events with the insulin products are rare and are similar among the various products.[1-17]

Hypoglycemia is the most common adverse event reported with insulin therapy. Because of the differences in onset and duration of action, the timing of hypoglycemia can vary between insulin formulations. Hypoglycemia risk may be increased when patients receive excessive doses of insulin, reduce their caloric intake, increase physical activity, during illnesses, or when receiving medications that increase the hypoglycemic effects of insulin.[1-17]

Redness, swelling, and itching at the injection site may result if administration is not done properly, if the skin is sensitive to cleansing solution, or if the patient is allergic to insulin or components of the insulin formulation.[1-17]

Generalized insulin allergies are rare but may present as a skin rash over the body, shortness of breath, fast pulse, sweating, a drop in blood pressure, bronchospasm, shock, anaphylaxis, or angioedema.[1-17]

A range of different chest symptoms were reported as adverse events associated with insulin therapy and were grouped under a nonspecific term chest pain.[1-17]

## VII. Dosing and Administration

The usual dosing regimens for the insulins are listed in Table 7. The dose of insulin is dependent upon the patient's glycemic response to food intake and exercise. Dose frequency and timing is dependent upon blood glucose levels, food consumption, time and level of exercise, as well as the insulin formulation used. Thus, an insulin regimen must be individualized to suit the specific needs and treatment goals of the patient.

**Table 7. Usual Dosing Regimens for the Insulins[1-17]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Rapid-Acting Insulins** | | | |
| Insulin aspart | Diabetes:<br>Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously.<br><br>SC injection: inject immediately (within 5 to 10 minutes) before a meal<br><br>CSII: approximately 50% of the total dose is usually given as meal-related boluses and the remainder is given as a basal | Insulin aspart has not been studied in pediatric patients younger than 2 years of age or in pediatric patients with type 2 diabetes.<br><br>Type 1 diabetes:<br>Dosage must be individualized. May be administered via SC injection and as CSII by external pump.<br><br>SC injection: inject immediately (within 5 to 10 minutes) before a | Cartridge:<br>100 U/mL<br><br>Pen:<br>100 U/mL<br><br>Vial:<br>100 U/mL |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | infusion. Pre-meal boluses of should be infused immediately (within 5 to 10 minutes) before a meal<br><br>IV: infuse at a concentration of 0.05 to 1.0 U/mL | meal<br><br>CSII: approximately 50% of the total dose is usually given as meal-related boluses and the remainder is given as a basal infusion. Pre-meal boluses of should be infused immediately (within 5 to 10 minutes) before a meal | |
| Insulin glulisine | Diabetes:<br>Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously.<br><br>SC injection: inject 15 minutes before a meal or within 20 minutes of starting a meal<br><br>CSII: dosage must be individualized<br><br>IV: infuse at a concentration of 0.05 to 1.0 U/mL | Insulin glulisine has not been studied in pediatric patients with type 1 diabetes younger than 4 years of age and in pediatric patients with type 2 diabetes.<br><br>Type 1 diabetes:<br>Dosage must be individualized. Approved for use in children for SC injections and for CSII by external pump, and intravenously<br><br>SC injection: 0.5 to 1.0 unit/kg/day administered 15 minutes before a meal or within 20 minutes of starting a meal<br><br>CSII: dosage must be individualized<br><br>IV: infuse at a concentration of 0.5 to 1.0 unit/mL | Pen:<br>100 U/mL<br><br>Vial:<br>100 U/mL |
| Insulin lispro | Diabetes:<br>Dosage must be individualized. May be administered via SC injection and CSII by external pump.<br><br>SC injection, CSII by external pump: 0.5 to 1 unit/kg/day; inject within 15 minutes before or immediately after a meal | Insulin lispro has not been studied in pediatric patients with type 1 diabetes younger than 3 years of age and in pediatric patients with type 2 diabetes.<br><br>Diabetes:<br>Dosage must be individualized. May be administered via SC injection and CSII by external pump.<br><br>SC injection, CSII by external pump: 0.5 to 1 unit/kg/day; inject within 15 minutes before or immediately after a meal | Cartridge:<br>100 U/mL<br><br>Pen:<br>100 U/mL<br><br>Vial:<br>100 U/mL |
| **Short-Acting Insulins** | | | |
| Insulin regular, human | Diabetes:<br>Dosage must be individualized. May be administered via SC injection and intravenously. | Insulin regular, human has not been studied in pediatric patients with type 1 diabetes younger than 2 years of age in pediatric patients with type 2 diabetes.<br><br>Diabetes: | Vial:<br>100 U/mL<br>500 U/mL |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | | Dosage must be individualized. May be administered via SC injection, CSII by external pump, and intravenously. | |
| **Intermediate-Acting Insulins** | | | |
| NPH, human insulin isophane | Diabetes:<br>Dosage must be individualized. May be administered via SC injection.<br><br>SC injection: 0.5 to 1 units/kg/day; administer in 2 divided daily doses and within 60 minutes of a meal | NPH, human insulin isophane has not been studied in pediatric patients younger than 12 years of age.<br><br>Diabetes:<br>Dosage must be individualized. May be administered via SC injection.<br><br>SC injection: 0.5 to 1 units/kg/day; administer in 2 divided daily doses and within 60 minutes of a meal | Pen:<br>300 U/3 mL<br><br>Vial:<br>100 U/mL |
| **Long-Acting Insulins** | | | |
| Insulin detemir | Diabetes:<br>Dosage must be individualized. May be administered via SC injection.<br><br>SC injection (type 1 diabetes): administer QD or BID<br><br>SC injection (type 2 diabetes): 10 units once daily in the evening or divided into a twice daily regimen | Insulin detemir has not been studied in pediatric patients younger than 2 years of age with type 1 diabetes and pediatric patients with type 2 diabetes.<br><br>Type 1 diabetes:<br>Dosage must be individualized. May be administered via SC injection.<br><br>SC injection: administer QD or BID | Pen:<br>100 U/ml<br><br>Vial:<br>300 U/3 mL |
| Insulin glargine, human recombinant analog | Diabetes:<br>Dosage must be individualized. May be administered via SC injection.<br><br>SC injection: administer QD at the same time every day; maintenance, 2 to 100 units/day | Insulin glargine, human recombinant analog has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes and pediatric patients with type 2 diabetes.<br><br>Type 1 diabetes:<br>Dosage must be individualized. May be administered via SC injection.<br><br>SC injection: administer QD at the same time every day; maintenance, 2 to 100 units/day | Pen:<br>300 U/3 mL<br><br>Vial:<br>100 U/mL |
| **Combination Insulins (Intermediate-Acting and Rapid-Acting)** | | | |
| Insulin aspart protamine and insulin aspart | Diabetes:<br>Dosage must be individualized. May be administered via SC injection.<br><br>SC injection: fixed ratio insulins are typically dosed on a | Safety and efficacy have not been established in pediatric patients. | Pen:<br>100 U (70-30)/mL<br><br>Vial:<br>100 U (70-30)/mL |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | BID basis (i.e., before breakfast and supper) with each dose intended to cover two meals or a meal and snack. May be injected within 15 minutes of meal initiation. | | |
| Insulin lispro protamine and insulin lispro | Diabetes Mellitus:<br>Dosage must be individualized. May be administered via SC injection.<br><br>May be injected within 15 minutes of meal initiation. | Safety and efficacy have not been established in pediatric patients. | Pen:<br>100 U (50-50)/mL<br>100 U (75-25)/mL<br><br>Vial:<br>100 U (50-50)/mL<br>100 U (75-25)/mL |
| **Combination Insulins (Intermediate-Acting and Short-Acting)** | | | |
| NPH, human insulin isophane and insulin regular, human | Diabetes Mellitus:<br>Dosage must be individualized. May be administered via SC injection. | NPH, human insulin isophane and insulin regular, human has not been studied in pediatric patients younger than 12 years of age.<br><br>Diabetes Mellitus:<br>Dosage must be individualized. May be administered via SC injection. | Pen:<br>100 U (70-30)/mL<br><br>Vial:<br>100 U (70-30)/mL |

BID=twice daily, CSII=Continuous Subcutaneous Insulin Infusion, IV=intravenous, QD=once daily, SC=subcutaneous

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the insulins are summarized in Table 8.

**Table 8. Comparative Clinical Trials with the Insulins**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Rapid-Acting and Short-Acting Insulin: Type 1 Diabetes Mellitus** | | | | |
| Home et al.[31] (2006)<br><br>Insulin aspart before meals and NPH insulin QD or BID<br><br>vs<br><br>regular insulin (REG) before meals and NPH insulin QD or BID<br><br>Insulin doses were adjusted to achieve target FPG and bedtime glucose 5.0-8.0 mmol/L and PPG <10.0 mmol/L. | ES, MC, MN, OL, PG, RCT<br><br>Patients ≥18 years of age with type 1 diabetes for at least 2 years on insulin for at least 1 year before inclusion, $HbA_{1c}$ ≤11.0%, BMI ≤35 kg/m$^2$ | N=753<br><br>36 months | Primary:<br>$HbA_{1c}$, hypoglycemia, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>At the end of the original six month study, $HbA_{1c}$ decreased in the insulin aspart group, with a statistically significant difference of -0.12 (95% CI, -0.22 to -0.03; P<0.02). At 30 months during the extension period, the difference of -0.16 in $HbA_{1c}$ was maintained (95% CI, -0.32 to -0.01; P<0.035). At 30 months, mean $HbA_{1c}$ was significantly lower in the insulin aspart group compared to the REG group after adjustment for the rate of hypoglycemic episodes and baseline $HbA_{1c}$ (P<0.001).<br><br>The RR estimate for major hypoglycemia was similar in both treatment groups at 36 months (RR, 1.0; 95% CI, 0.72 to 1.39; P value not significant). The proportion of patients reporting major hypoglycemia decreased from 16% in the first six months to 3% in the last six months in the insulin aspart group. The frequency of patients reporting major hypoglycemia also decreased in the REG group from 17 to 2%. There were no significant differences between groups in regards to major nocturnal hypoglycemia (RR, 0.89; 95% CI, 0.64 to 1.24; P value not significant).<br><br>The proportion of patients experiencing adverse events during the treatment period was similar in both treatment groups (P value not reported).<br><br>Secondary:<br>Not reported |
| Raskin et al.[32] (2000)<br><br>Insulin aspart before meals and NPH insulin QD | MC, OL, RCT<br><br>Type 1 diabetes patients with an $HbA_{1c}$ ≤11.0%, baseline $HbA_{1c}$ | N=882<br><br>6 months (with 6 month extension | Primary:<br>Effect on eight-point blood glucose measurements and $HbA_{1c}$ at six | Primary:<br>At six and 12 months, mean PPG (90 minutes postmeal) was significantly lower with insulin aspart compared to REG (P<0.05).<br><br>At six months, mean pre-prandial lunch and dinner blood glucose levels were significantly lower with insulin aspart when compared to REG |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| to BID<br><br>vs<br><br>regular insulin before meals and NPH insulin QD to BID<br><br>Doses of insulin were titrated to achieve FPG of 90-144 mg/dL, PPG ≤180 mg/dL and 2:00 AM blood glucose of 90-144 mg/dL. | 7.9% in the insulin aspart group and 7.95% in the REG group; patients were excluded if they had impaired hepatic, renal, or cardiac function; other exclusions included recurrent hypoglycemia, proliferative retinopathy, or total daily insulin requirement ≥1.4 units/kg | period) | and 12 months<br><br>Secondary:<br>Not reported | (P<0.05).<br><br>At 12 months, only pre-prandial dinner blood glucose levels were significantly lower with insulin aspart (P<0.05).<br><br>At six months, $HbA_{1c}$ was significantly lower with insulin aspart (7.78%) when compared to REG (7.93%; P=0.005).<br><br>At 12 months, $HbA_{1c}$ was significantly lower with insulin aspart (7.78%) when compared to REG (7.91%; P=0.005).<br><br>Mean NPH dose increased significantly with insulin aspart compared to REG (0.314 vs 0.296 U/kg; P=0.011).<br><br>Similar rates of hypoglycemia were observed in both treatment groups.<br><br>Secondary:<br>Not reported |
| Mathiesen et al.[33] (2007)<br><br>Insulin aspart before meals and NPH insulin QD to QID<br><br>vs<br><br>regular insulin before meals and NPH insulin QD to QID<br><br>Doses were titrated to achieve target goals FPG 4.1 to 6.1 | MC, OL, PG, RCT<br><br>Patients ≥18 years of age with insulin-treated type 1 diabetes for ≥12 months, either pregnant with a singleton pregnancy (gestational age ≤10 weeks) or planning to become pregnant, $HbA_{1c}$ ≤8.0% | N=412<br><br>28 months | Primary:<br>Major hypoglycemia during pregnancy<br><br>Secondary:<br>$HbA_{1c}$, self-measured eight-point plasma glucose profile, maternal adverse events, obstetric complications, diabetes complications | Primary:<br>The rates of major maternal hypoglycemia were lower in patients taking insulin aspart than patients taking REG. There was a 28% risk reduction for major hypoglycemia (RR, 0.720; 95% CI, 0.36 to 1.46; P value not reported) and a 52% risk reduction for major nocturnal hypoglycemia (RR, 0.48; 95% CI, 0.20 to 1.14; P value not reported) for patients taking insulin aspart than patients taking REG. However, this did not reach statistical significant.<br><br>Secondary:<br>Treatment with insulin aspart was as effective as treatment with REG in regards to $HbA_{1c}$ (mean difference, -0.04%; 95% CI, -0.18 to 0.11; P value not significant) during the second and third trimester (mean difference, -0.08%; 95% CI, -0.23 to 0.06; P value not significant).<br><br>Overall eight-point plasma glucose profiles were similar between treatment groups during the second and third trimesters. PPG levels were consistently lower in the insulin aspart group following breakfast than the REG group during the first trimester (P=0.044) and the third trimester |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| mmol/L, PPG<7.5 mmol/L, and $HbA_{1c}$ <6.5%. | | | | (P=0.0007). However, there was no difference in PPG after breakfast during the second trimester (P=0.153).<br><br>Both treatments were well tolerated and the adverse event profiles were similar between both groups. The frequency and profile of obstetric complications were similar between treatments with the most frequent complications being preeclampsia, threatened preterm labor, prolonged labor, and unplanned cesarean section. Treatment groups were not different in regards to changes in vital signs, physical examinations parameters, electrocardiograms, or clinical laboratory findings (P values were not reported). |
| Garg et al.[34] (2005)<br><br>Insulin glulisine before morning and evening meals and insulin glargine QD<br><br>vs<br><br>insulin glulisine after morning and evening meals and insulin glargine QD<br><br>vs<br><br>regular insulin before morning and evening meals and insulin glargine QD<br><br>Prandial insulin | MC, OL, PG, RCT<br><br>Patients with type 1 diabetes on insulin therapy for >1 year, baseline $HbA_{1c}$ 7.7% for both insulin glulisine treatment groups and 7.6% for the REG group | N=860<br><br>12 weeks | Primary:<br>Effect on $HbA_{1c}$, rate of hypoglycemia, and insulin dose<br><br>Secondary:<br>Not reported | Primary:<br>$HbA_{1c}$ reductions for insulin glulisine administered after meals (-0.11%) did not differ significantly from REG (-0.13%; P=0.6698).<br><br>$HbA_{1c}$ reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than REG (-0.13%; P=0.0234).<br><br>$HbA_{1c}$ reductions for insulin glulisine administered before meals (-0.26%) were significantly lower than insulin glulisine administered after meals (-0.11%; P=0.0062).<br><br>No significant differences were observed in the rates of symptomatic hypoglycemia (all and severe cases) between pre- and postmeal insulin glulisine and REG (P>0.05).<br><br>Change in total insulin dose from baseline was significantly higher in the REG group (2.35 U) compared to the premeal insulin glulisine group (0.04 U; P=0.014).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| doses were adjusted to achieve PPG of 120 to 160 mg/dL. | | | | |
| Dreyer et al.[35] (2005)<br><br>Insulin glulisine before meals and insulin glargine HS<br><br>vs<br><br>insulin lispro before meals and insulin glargine HS<br><br>Insulin doses were adjusted to achieve PPG of 120 to 160 mg/dL. | MC, OL, PG, RCT<br><br>Patients with type 1 diabetes on insulin therapy for >1 year, baseline $HbA_{1c}$ 7.6% for both treatment groups | N=672<br><br>26 weeks | Primary:<br>Effect on $HbA_{1c}$, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose<br><br>Secondary:<br>Not reported | Primary:<br>There was a comparable decrease in $HbA_{1c}$ between the insulin glulisine and insulin lispro groups (-0.14% for both groups; P value NS).<br><br>The incidences of all hypoglycemic events (nocturnal and severe) were similar between the two treatment groups.<br><br>Self-monitored blood glucose levels were similar in both treatment groups in regards to pre- and postprandial, bedtime and nocturnal blood glucose levels.<br><br>There was a significant increase in total insulin dose in the insulin lispro group (1.01 units) compared to the insulin glulisine group (-0.86 units; P=0.0123).<br><br>There was no significant difference in change in rapid-acting insulin dose between treatment groups.<br><br>Rates of hypoglycemia were similar in both treatment groups. Rates of adverse events were also similar among the two treatment groups.<br><br>Secondary:<br>Not reported |
| Philotheou et al.[36] (2011)<br><br>Premeal insulin glulisine<br><br>vs<br><br>premeal insulin | MC, NI, OL, PG, RCT<br><br>Patients 4 to 17 years of age with type 1 diabetes for ≥1 year with $HbA_{1c}$ between 6.0 to 11.0% who | N=570 (efficacy endpoints)<br><br>N=572 (safety endpoints)<br><br>26 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline at endpoint (study did not define "endpoint")<br><br>Secondary:<br>Proportion of | Primary:<br>The adjusted mean change in $HbA_{1c}$ from baseline to endpoint was 0.10±0.08% with insulin glulisine and 0.16±0.07% with insulin lispro. The difference between the two groups was -0.06% (95% CI, -0.24 to 0.12; P value not reported), showing non-inferiority of insulin glulisine compared to insulin lispro based on the prespecified non-inferiority margin of 0.4%.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| lispro<br><br>All patients received NPH BID or insulin glargine QD.<br><br>Rapid-acting and basal insulin doses were titrated to achieve age-specific FPG goal of 100 to 140 mg/dL (<8 years old) or 90 to 140 mg/dL (≥8 years old) and PPG goal of 120 to 180 mg/dL (<8 years old) or 100 to 160 mg/dL (≥8 years old) using blood-referenced blood glucose meters. | were receiving insulin therapy for ≥1 year with NPH insulin or insulin glargine as basal insulin | (plus a 24-hour follow-up period) | patients who reached target $HbA_{1c}$, change in $HbA_{1c}$ from baseline at 12 and 26 weeks, self-monitored FPG, PPG and pre-prandial glucose, insulin doses, symptomatic hypoglycemia between 12 and 26 weeks and safety | At baseline, 33.2 and 33.3% of patients had $HbA_{1c}$ at goal in the insulin glulisine and insulin lispro groups, respectively. At endpoint, the percentage of patients with $HbA_{1c}$ at goal was 38.4% with insulin glulisine and 32.0% with insulin lispro (P=0.039).<br><br>Change in $HbA_{1c}$ with insulin glulisine and insulin lispro was -0.01±0.07% and -0.03±0.06% at 12 weeks and 0.08±0.08% and 0.17±0.08% at 26 weeks, respectively (P values not reported).<br><br>At endpoint, self-monitored FPG was lower in the insulin glulisine group compared to the insulin lispro group (158.0±3.8 vs 170.5±3.7 mg/dL; P=0.014). Baseline FPG, PPG and pre-prandial glucose as well as endpoint PPG and pre-prandial glucose were comparable between the two groups.<br><br>Total daily insulin doses increased by 0.01±0.01 units/kg with insulin glulisine and by 0.05±0.01 units/kg with insulin lispro (P=0.0045).<br><br>The monthly rate of symptomatic hypoglycemia per patient was 3.10±4.33 and 2.91±4.35 with insulin glulisine and insulin lispro, respectively (P value not reported). No difference was seen with the two groups in severe, nocturnal or severe nocturnal symptomatic hypoglycemia.<br><br>The frequency and type of treatment-emergent adverse events or serious adverse events were similar between the treatment groups. |
| van Bon et al.[37] (2011)<br><br>Insulin glulisine<br><br>vs<br><br>insulin aspart<br><br>vs | MC, OL, RCT, XO<br><br>Patients ≥18 years of age with type 1 diabetes treated with insulin for ≥2 years and continuous SC insulin infusion for ≥6 months, | N=256<br><br>39 weeks (13 weeks of treatment period for each study medication) | Primary: Unexplained hyperglycemia (>300 mg/dL) and/or perceived infusion set occlusion<br><br>Secondary: Unexplained hyperglycemia, | Statistical significant was defined as P <0.025 in this study.<br><br>Primary:<br>Percentage of patients with at least one unexplained hyperglycemia and/or perceived infusion set occlusion was comparable between insulin glulisine and insulin aspart (68.4 vs 62.1%; P=0.04) and between insulin glulisine and insulin lispro (68.4 vs 61.3%; P=0.03).<br><br>Secondary:<br>Percentage of patients reporting at least one unexplained hyperglycemia was similar when comparing insulin glulisine (61.3%) to insulin aspart |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| insulin lispro<br><br>Insulin doses were titrated to achieve PPG <180 mg/dL and pre-prandial glucose between 90 to 130 mg/dL. | requiring ≤90 units/day of insulin, with $HbA_{1c}$ <8.5% and BMI<35 kg/m$^2$ | | perceived infusion set occlusion, $HbA_{1c}$, proportion of patients with $HbA_{1c}$ <7.0%, seven-point plasma glucose profiles, hypoglycemic episodes, episodes of asymptomatic ketonemia and ketoacidosis, insulin doses, time to infusion set change, infusion site reactions and serious adverse reactions | (55.9%; P=0.08) and insulin lispro (56.3%; P=0.11).<br><br>No significant difference was seen in the percentage of patients with at least one perceived infusion set occlusion between insulin glulisine and insulin aspart (32.8 vs 27.0%; P=0.08) and between insulin glulisine and insulin lispro (32.8 vs 27.0; P=0.06).<br><br>$HbA_{1c}$ remained stable from baseline at the end of treatment period with all three insulin groups, with no significant differences seen among groups.<br><br>Similar percentage of patients achieved $HbA_{1c}$ <7.0% in the insulin glulisine, insulin aspart and insulin lispro groups (28, 31 and 30%, respectively; P values not reported).<br><br>The seven-point plasma glucose profiles were similar among all three groups at baseline. At the end of treatment, after-lunch glucose was higher with insulin glulisine compared to insulin aspart (166.1 vs 155.5 mg/dL; P=0.021), and midnight glucose was higher with insulin lispro compared to insulin glulisine (159.4 vs 148.1 mg/dL; P=0.018).<br><br>The overall rate of symptomatic hypoglycemia per patient-year was higher with insulin glulisine (73.8) compared to insulin aspart (65.0; P=0.008) and insulin lispro (62.7; P<0.001).<br><br>The monthly rate of significant hyperketonemia and/or hyperketonemia at risk for ketosis was higher with insulin glulisine (0.14) compared to insulin aspart (0.06; P=0.01) and insulin lispro (0.06; P=0.02). One patient was hospitalized for diabetic ketoacidosis while receiving insulin glulisine.<br><br>Insulin doses remained stable throughout the study. No significant differences were seen among the three groups in time to infusion set change, frequency of infusion site reactions and serious adverse reactions. No death was reported. |
| Rave et al.[38] (2006) | 4-way XO, OL, RCT, single-dose | N=21 | Primary:<br>Blood glucose | Primary:<br>Blood glucose exposure within two hours after the start of a meal was |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Premeal insulin glulisine (2 minutes prior to a standardized 15-minute meal)<br><br>vs<br><br>postmeal insulin glulisine (15 minutes postmeal)<br><br>vs<br><br>premeal regular insulin (30 minutes premeal)<br><br>vs<br><br>premeal regular insulin (2 minutes premeal) | Patients 18 to 55 years of age with type 1 diabetes on the same insulin regimen for ≥2 months before enrollment, BMI 18 to 32 kg/m$^2$, $HbA_{1c}$ <10.0%, serum C-peptide levels ≤0.9 ng/mL | 4 treatment periods | exposure and excursion at two and six hours following a meal, mean maximum blood glucose concentration, time to reach mean maximum blood glucose concentration<br><br>Secondary:<br>Not reported | significantly lower with insulin glulisine than with REG (279 vs 344 mg·h/dL, respectively; P value not reported). However, at six hours following a meal, blood glucose exposure was not significantly different between both groups (708 vs 770 mg·h/dL, respectively; P value not reported).<br><br>When insulin glulisine was given immediately prior to a meal and REG 30 minutes prior to the meal, blood glucose control was comparable. Both two- and six-hour blood glucose exposures were well matched. However, treatment with REG resulted in time to maximum blood glucose excursion to occur 43 minutes later compared to insulin glulisine.<br><br>Postmeal insulin glulisine and REG given immediately premeal produced similar effects on PPG exposure and excursion at two hours after a meal (337 vs 334 mg·h/dL, respectively) and six hours after a meal (777 vs 770 mg·h/dL, respectively; P values not reported).<br><br>Insulin glulisine was absorbed more rapidly than REG and reached a mean maximum concentration that was almost twice as large as the mean maximum concentration for REG (P value was not reported).<br><br>In addition, the time to reach maximum concentration for insulin glulisine was half that of REG (P value was not reported).<br><br>Secondary:<br>Not reported |
| Anderson et al.[39] (1997)<br><br>Insulin lispro before each meal and basal insulin for 3 months<br><br>vs<br><br>Regular insulin | MC, OL, RCT, XO<br><br>Patients with type 1 diabetes previously treated with REG, baseline $HbA_{1c}$ 8.5% for both groups | N=1,008<br><br>6 months | Primary:<br>Effect on postprandial serum glucose (one- and two-hour), $HbA_{1c}$, and frequency of hypoglycemia<br><br>Secondary:<br>Effect on insulin | Primary:<br>One-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (12.9 vs 13.9 mmol/L; P<0.001).<br><br>Two-hour postprandial serum glucose rise was significantly lower with insulin lispro compared to REG (11.2 vs 12.9 mmol/L; P<0.001).<br><br>There was no difference in $HbA_{1c}$ reduction between the two treatment groups.<br><br>The rate of hypoglycemia was 12% less during treatment with insulin |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (REG) before each meal and basal insulin for 3 months | | | dose, frequency of premeal and basal insulin injections, and weight | lispro when compared to REG (P<0.001).<br><br>Secondary:<br>A small but significant increase in total insulin dose was observed with insulin lispro when compared to REG (0.71 vs 0.69 U/kg; P<0.001).<br><br>No significant difference was reported for frequency of premeal injections between the two treatment groups.<br><br>Significantly less patients on REG required ≥2 basal insulin injections compared to insulin lispro (46.4 vs 44.0%; P<0.05).<br><br>There were no significant differences in weight gain between the two treatment groups.<br><br>There were no differences in type and frequency of adverse events between the two treatments. |
| Fairchild et al.[40] (2000)<br><br>Insulin lispro and NPH or Lente insulin for 3 months<br><br>vs<br><br>regular insulin (REG) and NPH or Lente insulin for 3 months<br><br>Insulin doses were titrated to achieve $HbA_{1c}$ 6.0 to 8.0% and preprandial blood glucose levels 4- | OL, RCT, XO<br><br>Children 5 to 10 years of age with type 1 diabetes for at least 12 months, prepubertal, on BID insulin, attending the Diabetes Clinics at the New Children's Hospital, Newcastle | N=43<br><br>6 months | Primary:<br>$HbA_{1c}$<br><br>Secondary:<br>Blood glucose levels before and after meals, two-hour PPG excursions, hypoglycemic events | Primary:<br>After three months, change in $HbA_{1c}$ was not significantly different between patients on insulin lispro and patients on REG (mean difference, -0.19±0.63%; P value not reported).<br><br>Secondary:<br>There were no significant differences in blood glucose levels before or after meals and two-hour PPG excursions. However, the 3 AM blood glucose levels were significantly lower in patients taking REG than in patients taking insulin lispro (mean difference between treatments, -2.35 mmol/L; 95% CI, -3.98 to -0.72; P=0.01).<br><br>There was no significant difference in the frequency of total hypoglycemic episodes or hypoglycemic episodes with a blood glucose <3 mmol/L between patients taking REG and patients taking insulin lispro (P value was not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| 10 mmol/L. | | | | |
| Mortensen et al.[41] (2006)<br><br>Premeal biphasic insulin aspart (BIAsp) 30 plus NPH insulin at bedtime (HS)<br><br>vs<br><br>premeal REG (before lunch and dinner) plus biphasic human insulin (BHI) 30 before breakfast and NPH insulin HS<br><br>Insulin doses were titrated to achieve target FPG <8 mmol/L and PPG <10 mmol/L. | MN, OL, PG, RCT<br><br>Adolescents 10 to 17 years of age with type 1 diabetes for at least 18 months | N=167<br><br>16 weeks | Primary:<br>$HbA_{1c}$, change in PPG, body weight, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>$HbA_{1c}$ decreased by about -0.2% in both treatment arms at endpoint. There was no significant difference in the change of $HbA_{1c}$ between groups at study endpoint (P=0.62).<br><br>At 16 weeks, both the biphasic insulin aspart group and REG group had reductions in average PPG (SEM, 0.37 and 0.77, respectively; P=0.47).<br><br>The increase in body weight was smaller in the biphasic insulin aspart group than the REG group. The difference between groups was significant for males (P=0.007), but not for females.<br><br>The rates of hypoglycemia during the day and during the night were similar between treatment groups (P value was not reported).<br><br>Secondary:<br>Not reported |
| Chen et al.[33] (2006)<br><br>Biphasic insulin aspart 30 (BIAsp30) TID, divided in a 30:30:40 ratio for 12 weeks; NPH could also be added at bedtime | OL, RCT, XO<br><br>Patients ≥18 years of age with type 1 diabetes for ≥12 months, previously treated with soluble human insulin TID plus NPH at bedtime with a total daily | N=27<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline at end of each 12 week-treatment period, daily seven-point self monitoring of blood glucose<br><br>Secondary: | Primary:<br>Eleven out of 27 patients chose to take bedtime NPH while they were being treated with insulin aspart.<br><br>Both the biphasic insulin aspart and the REG groups had significant improvement in $HbA_{1c}$ levels from baseline (P<0.01). However, the biphasic insulin aspart group had a significantly greater reduction in $HbA_{1c}$ than that of the REG group (P<0.05). Upon further analysis it was ascertained that most of the between-group difference in $HbA_{1c}$ was driven by the patients who administered bedtime NPH in combination with their TID biphasic insulin aspart. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>REG insulin administered TID plus NPH insulin at bedtime for 12 weeks<br><br>Doses were titrated to achieve FPG 5.0 to 8.0 mmol/L and PPG 5.0 to 10.0 mmol/L. | dose <1.8 IU/kg, BMI <35 kg/m$^2$ and $HbA_{1c}$ ≥8.0% during the last 6 months; at 12 weeks, patients were switched to the alternative insulin regimen for another 12 weeks | | Hypoglycemia | Both the biphasic insulin aspart and the REG groups had similar results in self monitoring of blood glucose of daytime glycemic control. However, the biphasic insulin aspart group had significantly lower blood glucose concentrations at two hours after dinner and at bedtime in comparison to the REG group (P<0.05).<br><br>Secondary:<br>The rates of hypoglycemia (events/patient-week) were similar among the biphasic insulin aspart and REG group (1.2 vs 0.7, respectively for total events and 0.2 vs 0.2, respectively for nocturnal events; P value not reported). |
| **Rapid-Acting and Short-Acting Insulin Administered By Continuous Subcutaneous Insulin Infusion (CSII): Type 1 Diabetes Mellitus** | | | | |
| Bode et al.[43] (2002)<br><br>Insulin aspart (IAsp) administered by CSII via external pump<br><br>vs<br><br>insulin lispro administered by CSII via external pump<br><br>vs<br><br>regular insulin (BR) administered by CSII via external pump | MC, OL, PG, RCT<br><br>Patients 18 to 71 years of age with type 1 diabetes with fasting C-peptide <0.5 ng/mL who had been treated with CSII therapy continuously for the previous 3 months | N=146<br><br>16 weeks | Primary:<br>$HbA_{1c}$, eight-point self monitoring blood glucose, weight, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>After 16 weeks of treatment, the mean change in $HbA_{1c}$ from baseline was not significantly different among the three groups (0.00%, 0.15%, and 0.18% for the IAsp, BR, and lispro groups, respectively).<br><br>For the eight-point self monitoring blood glucose evaluation, postprandial values for subjects in the rapid-acting insulin analog groups were improved from baseline values and tended to be lower than those for subjects in the BR group. A few statistically significant differences were observed at week 16 between the treatment groups: dinner +90 minutes, the blood glucose value for the IAsp group was lower than those for BR and lispro groups (P=0.019); at 2:00 A.M., the blood glucose value for the BR group was lower than those for IAsp and lispro groups (P=0.002).<br><br>Mean weight did not significantly increase or decrease during the study among the treatment groups.<br><br>Similar numbers of subjects (≥90%) in each treatment group reported one or more minor hypoglycemic episodes. The rate of confirmed hypoglycemia was not significantly different between treatment groups. The rate of confirmed nocturnal hypoglycemia for the IAsp group was |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | lower than that for the BR group and similar to that of the lispro group. No major nocturnal hypoglycemic episodes occurred during the study.<br><br>Secondary:<br>Not reported |
| Weinzimer et al.[44] (2008)<br><br>Insulin aspart administered by CSII via external pump<br><br>vs<br><br>insulin lispro administered by CSII via external pump | MC, OL, PG, RCT<br><br>Patients 3 to 18 years of age with type 1 diabetes for ≥1 year and $HbA_{1c}$ ≤10.0% who were being treated with either insulin aspart or insulin lispro by CSII for ≥3 months | N=298<br><br>16 weeks | Primary:<br>$HbA_{1c}$ at week 16<br><br>Secondary:<br>FPG, eight-point self monitoring blood glucose, weight, hypoglycemia | Primary:<br>At study end point, the mean $HbA_{1c}$ values were 7.9% and 8.1% (last observation carried forward) for insulin aspart and insulin lispro, respectively. The change in $HbA_{1c}$ from baseline to week 16 was -0.15% in the insulin aspart group and -0.05% in the insulin lispro group (95% CI, -0.27 to 0.07).<br><br>After 16 weeks, 59.7% of patients in the insulin aspart group and 43.8% of the patients in the insulin lispro group achieved American Diabetes Association age-specific recommendations for $HbA_{1c}$ (P=0.040).<br><br>Secondary:<br>After 16 weeks, mean FPG were similar among the treatment groups (insulin aspart 166.5 mg/dl; lispro 180.2 mg/dl; P=0.113).<br><br>The eight-point self monitoring blood glucose profiles collected before weeks 0 and 16 showed a similar pattern for both treatment groups. No significant differences between treatment groups in mean self monitoring blood glucose values were observed at any of the eight time points at week 16.<br><br>Mean body weight increased from baseline for both treatment groups during the trial, but was comparable between treatment groups (insulin aspart 1.8 kg; insulin lispro 1.6 kg; P=0.387).<br><br>Rates of minor and major hypoglycemic episodes were similar between the two treatment groups. A similar percentage of patients reported at least one major hypoglycemic event during the study period (9.6 and 8.0% in the insulin aspart and insulin lispro groups, respectively). Rates of nocturnal hypoglycemic events were also similar between the treatment groups. |
| Colquitt et al.[45] | MA | N=577 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (2003)<br><br>Rapid-acting insulin analogs administered by CSII<br><br>vs<br><br>regular insulin administered by CSII | Analysis of 6 randomized trials that compared rapid-acting insulin analogs vs REG in the treatment of patients with diabetes using continuous infusions; trials less than 10 weeks in duration were excluded | Duration varied | Effect in $HbA_{1c}$, insulin dose, weight change, patient preference, quality of life and adverse events<br><br>Secondary:<br>Not reported | Significant improvement in $HbA_{1c}$ of -0.26% (95% CI, -0.47 to -0.06; P=0.01) was observed with insulin lispro compared to REG.<br><br>The differences in $HbA_{1c}$ from baseline between insulin aspart, REG, or insulin lispro were not significant.<br><br>No significant difference in insulin dose was reported between treatment groups.<br><br>No significant difference in weight was reported between treatment groups.<br><br>Two studies reported patient preference to short-acting insulin analogs. One study found no difference in satisfaction between treatment groups and one study found greater patient satisfaction towards short-acting insulin analogs.<br><br>No difference in frequency of severe hypoglycemic events was reported between treatment groups.<br><br>Secondary:<br>Not reported |
| **Rapid-Acting and Short-Acting Insulin: Type 2 Diabetes Mellitus** | | | | |
| McSorley et al.[46] (2002)<br><br>Biphasic insulin aspart (BIAsp) 30 BID for 2 weeks<br><br>vs<br><br>biphasic human insulin (BHI) 30 BID for 2 weeks<br><br>Patients were XO | 2-period, DB, RCT, XO<br><br>Patients 40 to 75 years of age with type 2 diabetes for at least 1 year, had been on BID biphasic human insulin 30 for at least 6 months | N=13<br><br>4 weeks | Primary:<br>AUC during two hours following insulin administration at dinner and breakfast<br><br>Secondary:<br>Maximum serum insulin concentration after two injections; time | Primary:<br>The AUC two hours following insulin administration was significantly greater for biphasic insulin aspart 30 than for biphasic human insulin 30 after dinner and breakfast (P<0.05).<br><br>Secondary:<br>Biphasic insulin aspart 30 reached a maximum concentration that was 18% higher after dinner and 35% higher after the following day's breakfast than that of biphasic human insulin 30 (P<0.05 for both values).<br><br>The time taken to reach peak serum insulin concentrations was one hour earlier after breakfast and 45 minutes earlier after dinner in the biphasic insulin aspart 30 group compared to the biphasic human insulin 30 group. However, the only measure to reach statistical significance was after |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| to other insulin regimen after 2 weeks of initial randomized insulin regimen. | | | to reach peak serum insulin concentrations; four-hour glucose excursion following dinner, breakfast, and lunch; glucose maximum concentration after dinner, breakfast, and lunch; time taken to reach glucose maximum concentration values | breakfast (P<0.05).<br><br>Serum glucose excursions were significantly lower in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group after dinner (P<0.05) and after breakfast (P<0.05). However, serum glucose excursion after lunch was significantly higher in the biphasic insulin aspart 30 group than the biphasic human insulin 30 group (P<0.05).<br><br>Following breakfast, glucose maximum concentration was significantly lower and time to reach glucose maximum concentration was significantly earlier with biphasic insulin aspart 30 than biphasic human insulin 30 (P<0.05 for both measures).<br><br>Both insulins were well-tolerated and had comparable adverse events. There were no major hypoglycemic episodes or serious adverse events reported. |
| Bretzel et al.[47] (2004)<br><br>Insulin aspart before meals and NPH insulin QD (if needed)<br><br>vs<br><br>regular insulin before meals and NPH insulin QD (if needed)<br><br>vs<br><br>NPH/REG insulin 70/30 mix QD to | MC, OL, PG, RCT<br><br>Adult (≥35 years old) type 2 diabetes with $HbA_{1c}$ ≤10.0%, baseline $HbA_{1c}$ 7.82% for insulin aspart, 7.83% for REG and 7.78% for the premixed insulin | N=231<br><br>12 weeks | Primary:<br>Equivalence of the primary efficacy endpoint–effect on $HbA_{1c}$<br><br>Secondary:<br>Not reported | Primary:<br>Insulin aspart reduced $HbA_{1c}$ by -0.91±1.00%, while REG reduced $HbA_{1c}$ by -0.73±0.87% and premixed insulin reduced $HbA_{1c}$ by -0.65±1.10%.<br><br>Insulin aspart was found not to be statistically equivalent to REG (P=0.025) or the premixed insulin formulation (P=0.092). Significance level for P was set at 0.0083.<br><br>The proportion of patients reporting an adverse event was comparable in all three treatment groups.<br><br>The proportion of patients that experienced a hypoglycemic event (41% for insulin aspart and REG and 30% for premixed insulin) was not statistically different.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| BID<br><br>Insulin doses were titrated to achieve blood glucose levels of 80 to 110 mg/dL. | | | | |
| Niskanen et al.[48] (2004)<br><br>Insulin aspart 30% and insulin aspart protamine 70% administered via proprietary pen for 12 weeks<br><br>vs<br><br>insulin lispro 25% and insulin lispro protamine 75% administered via proprietary pen for 12 weeks | MC, OL, RCT, XO<br><br>Patients with type 2 diabetes previously treated with insulin with $HbA_{1c}$ <12.0%, baseline $HbA_{1c}$ for the whole sample size was 8.5% | N=137<br><br>24 weeks | Primary:<br>Effect on $HbA_{1c}$ and seven-point blood glucose levels<br><br>Secondary:<br>Patient satisfaction with the pen devices | Primary:<br>$HbA_{1c}$ reduction was comparable between the two treatment groups.<br><br>The seven-point blood glucose profile was comparable at each time point and there was no significant difference between the two treatment groups.<br><br>Secondary:<br>Significantly more patients preferred the insulin aspart pen device compared to the insulin lispro pen device (P<0.005).<br><br>The incidence of reported adverse events was similar between treatment groups. |
| Dailey et al.[49] (2004)<br><br>Insulin glulisine before meals BID (AM and PM) and NPH insulin BID<br><br>vs<br><br>regular insulin before meals BID | MC, OL, PG, RCT<br><br>Patients with type 2 diabetes on continuous insulin therapy for ≥6 months, baseline $HbA_{1c}$ 7.58% for insulin glulisine and 7.52% for REG | N=876<br><br>26 weeks | Primary:<br>Effect on $HbA_{1c}$, rate of hypoglycemia, effect on self-monitored blood glucose and insulin dose<br><br>Secondary:<br>Not reported | Primary:<br>There was a small, but significantly greater decrease in $HbA_{1c}$ observed in the insulin glulisine group compared to the REG group (-0.46 vs -0.30%; P=0.0029).<br><br>No significant differences were observed in either group in the incidence of hypoglycemia.<br><br>Significantly lower two-hour PPG (breakfast and dinner) was observed in the insulin glulisine group compared to the REG group (P<0.05).<br><br>There was no significant difference in total daily insulin doses between |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (AM and PM) and NPH insulin BID<br><br>Insulin doses were adjusted to achieve PPG 120 to 160 mg/dL. | | | | the two treatment groups throughout the study.<br><br>Secondary:<br>Not reported |
| Rayman et al.[50] (2007)<br><br>Insulin glulisine and NPH insulin BID, in addition to current oral antidiabetic agents<br><br>vs<br><br>Regular insulin and NPH insulin BID, in addition to current oral antidiabetic agents<br><br>Insulin glulisine and regular doses were adjusted to achieve target PPG 120 to 160 mg/dL.<br><br>NPH insulin was titrated to achieve FPG 90 to 120 mg/dL. | MC, MN, OL, PG, RCT<br><br>Patients aged ≥18 years of age with type 2 diabetes on >6 months of continuous insulin treatment prior to study entry, $HbA_{1c}$ 6.0 to 11.0%, ability and willingness for self monitoring of blood glucose | N=892<br><br>26 weeks | Primary:<br>Change in $HbA_{1c}$, adverse events<br><br>Secondary:<br>Difference in the change of $HbA_{1c}$ at 12 and 26 weeks between insulin glulisine and REG, self-monitored seven-point blood glucose profile, symptomatic hypoglycemia, insulin dose | Primary:<br>$HbA_{1c}$ decreased from baseline to study endpoint in both the insulin glulisine and REG groups. $HbA_{1c}$ in the insulin glulisine group decreased from 7.58±0.90% to 7.25±0.95% and from 7.50±0.89% to 7.19±0.90% in the REG group (P value not reported). No difference between groups was seen in the proportion of patients achieving $HbA_{1c}$ levels ≤7.0% (P=0.8962).<br><br>There was no between-treatment difference in the frequency and type of treatment emergent adverse events observed (P value not reported).<br><br>Secondary:<br>There was no between-treatment difference in change in $HbA_{1c}$ for insulin glulisine and REG at 12 weeks and study endpoint (P=0.3573 and P=0.5726, respectively).<br><br>At study endpoint, glucose values were significantly lower two hours postbreakfast with insulin glulisine compared to REG (P<0.001).<br><br>There were no noteworthy differences between both treatment groups in the frequencies and monthly rates of all symptomatic hypoglycemia. However, the frequencies and monthly rates of severe symptomatic hypoglycemia were lower in the insulin glulisine group than the REG group. Patients taking insulin glulisine also had fewer reports of nocturnal symptomatic hypoglycemia from month four to treatment end compared to patients taking REG (P=0.029).<br><br>In terms of insulin doses, there was a larger increase in the short-acting dose with REG than with insulin glulisine (adjusted mean, 4.47 vs 2.95 U, respectively; P=0.0645). Overall, the total daily insulin dose |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | increased slightly more with REG. However, the difference was not significant (P=0.1727). |
| Rosenstock et al.[51] (2008)<br><br>Basal bolus therapy (BBT) (premeal insulin lispro and insulin glargine HS)<br><br>vs<br><br>premeal premixed therapy (PPT) (lispro mix 50/50 TID) | MC, NI, OL, RCT<br><br>Patients with type 2 diabetes | N=374<br><br>24 weeks | Primary:<br>$HbA_{1c}$, percentage of patients achieving $HbA_{1c}$ <7.0%, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>$HbA_{1c}$ was reduced significantly from baseline in both treatment groups (P<0.0001). At 24 weeks, $HbA_{1c}$ was lower with basal bolus therapy compared to premeal premixed therapy (6.78 vs 6.95%, respectively; P=0.021). The difference between treatment groups was -0.22% (90% CI, -0.38 to -0.07; P value not reported).<br><br>The percentage of patients achieving an $HbA_{1c}$ <7.0% was 54 vs 69% in the premeal premixed therapy and basal bolus therapy groups, respectively (P=0.009).<br><br>Rates of hypoglycemia were similar between both treatment groups.<br><br>Secondary:<br>Not reported |
| **Rapid-Acting and Short-Acting Insulin: Type 1 and Type 2 Diabetes Mellitus** | | | | |
| Vignati et al.[52] (1997)<br><br>Insulin lispro and NPH insulin BID before meals for 2 months<br><br>vs<br><br>regular insulin and NPH insulin BID before meals for 2 months<br><br>Doses of both regimens were adjusted to | MC, OL, RCT, XO<br><br>Patients with type 1 diabetes and type 2 diabetes previously treated with REG and NPH, baseline $HbA_{1c}$ 8.0% for both groups in patients with type 1 diabetes and 8.1% for both groups in patients with type 2 diabetes | N=707<br><br>4 months | Primary:<br>Effect on $HbA_{1c}$, pre-prandial glucose levels, PPG levels and frequency of hypoglycemia, and insulin dose<br><br>Secondary:<br>Not reported | Primary:<br>There was no significant difference in $HbA_{1c}$ reduction between the two treatment groups (P>0.648).<br><br>Pre-prandial glucose levels did not differ significantly between the two treatment groups for any meal (P≥0.066) or at bedtime (P>0.404).<br><br>PPG was significantly lower with insulin lispro compared to REG for the morning meal (8.6 vs 9.8 mmol/L; P<0.001) and the evening meal (8.6 vs 9.6 mmol/L; P<0.005) for type 1 diabetics. No significant difference was noted in the noon meal.<br><br>PPG was significantly lower with insulin lispro compared to REG in the morning meal only in type 2 diabetics (9.5 vs 10.4 mmol/L; P<0.001).<br><br>There was no significant difference in hypoglycemic events between the two treatment groups (P=0.677 for type 1 diabetics and P=0.419 for type 2 diabetics). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| achieve 2-hour postprandial serum glucose ≤160.2 mg/dL and fasting serum glucose ≤140.0 mg/dL. | | | | Endpoint insulin dose was significantly higher with insulin lispro compared to regular human insulin in type 1 diabetics albeit the difference was small (0.63 vs 0.60 U/kg; P=0.015). There were no significant differences in insulin doses in type 2 diabetics.<br><br>Secondary:<br>Not reported |
| Anderson et al.[53] (1997)<br><br>Insulin lispro before meals and basal insulin<br><br>vs<br><br>regular insulin before meals and basal insulin | MC, OL, RCT<br><br>Patients with type 1 diabetes and type 2 diabetes previously treated with REG, baseline $HbA_{1c}$ 8.2% for both groups in patients with type 1 diabetes and baseline $HbA_{1c}$ 8.9% for REG and 8.7% for insulin aspart | N=631<br><br>12 months | Primary:<br>Effect on $HbA_{1c}$, postprandial rise in serum glucose, frequency of hypoglycemia, and insulin dose<br><br>Secondary:<br>Not reported | Primary:<br>$HbA_{1c}$ was significantly lower with insulin lispro compared to REG in type 1 diabetics (8.1 vs 8.3%; P<0.05). There was no difference in $HbA_{1c}$ between treatment groups for type 2 diabetics.<br><br>Postprandial (two-hour) serum glucose rise was significantly reduced with insulin lispro compared to REG in type 1 diabetics (64%; P=0.007) and type 2 diabetics (48%; P=0.004).<br><br>There was no difference in rates of hypoglycemia between the two treatment groups.<br><br>There was a small, but significant reduction in premeal insulin dose in the insulin lispro group (-0.03 U/kg; P=0.004) but a small and significant increase in the basal insulin dose (0.05 U/kg; P<0.001) in type 1 diabetics. There were no dose changes in the REG group.<br><br>For type 2 diabetics, the daily dose increase of insulin was comparable between the treatment groups.<br><br>Secondary:<br>Not reported |
| Plank et al.[54] (2005)<br><br>Short-acting insulin analogs (insulin lispro and/or insulin | MA<br><br>Analysis of 42 randomized trials that compared short-acting insulin analogs vs | N=7,933<br><br>Duration varied | Primary:<br>Effect on $HbA_{1c}$ and number of hypoglycemic episodes<br><br>Secondary: | Primary:<br>A small but significant difference in $HbA_{1c}$ was observed with short-acting insulin analogs compared to REG in type 1 diabetes (-0.12%; 95% CI, -0.17 to -0.07).<br><br>No significant differences in $HbA_{1c}$ were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (- |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| aspart)<br><br>vs<br><br>regular insulin | REG in the treatment of type 1 diabetes and type 2 diabetes patients | | Quality of life, pregnancy outcomes, and adverse events | 0.02%; 95% CI, -0.10 to 0.07).<br><br>No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in type 1 diabetic patients (-0.05 episodes/patient/month; 95% CI, -0.22 to 0.11).<br><br>No significant differences in hypoglycemic rates were observed with short-acting insulin analogs compared to REG in patients with type 2 diabetes (-0.04 episodes/patient/month; 95% CI, -0.12 to 0.04).<br><br>Secondary:<br>Quality of life reported in type 1 diabetes favored short-acting insulin analogs in four studies and found no difference in three studies. No significant difference in quality of life was reported in studies with type 2 diabetics (two studies total).<br><br>There were no significant differences in maternal or fetal outcomes between the two insulin groups.<br><br>Comparable incidence and type of adverse events were reported for both insulin groups. |
| Siebenhofer et al.[55] (2006)<br><br>Rapid-acting insulin analogs (insulin lispro, insulin aspart, insulin glulisine)<br><br>vs<br><br>regular insulin | MA<br><br>Analysis of 49 randomized trials that compared rapid-acting insulin analogs to REG in patients with type 1 diabetes and type 2 diabetes | N=8,274<br><br>Duration varied | Primary:<br>$HbA_{1c}$, hypoglycemia<br><br>Secondary:<br>Adverse events | Primary:<br>In patients with type 1 diabetes, the WMD in $HbA_{1c}$ was estimated to be -0.1% (95% CI, -0.2 to -0.1; P=0.01) in favor of insulin analogs compared to REG. In the subgroup analyses, results were divided into patients taking continuous SC insulin injections and patients taking conventional intensified insulin therapy. In patients taking continuous SC insulin therapy compared to REG, the WMD in $HbA_{1c}$ was -0.2 (95% CI, -0.3 to -0.1; P value not reported) and in patients taking intensified insulin therapy compared to REG, the WMD was -0.1% (95% CI, -0.1 to 0.0; P value not reported).<br><br>In patients with type 2 diabetes, the WMD of $HbA_{1c}$ was estimated to be 0.0% (95% CI, -0.1 to 0.0). None of the studies evaluating differences in $HbA_{1c}$ between insulin analogs and REG showed significant differences (P values not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | In children, adolescents, pregnant patients with type 1 diabetes, there were no significant reductions in $HbA_{1c}$ (P values were not reported).<br><br>The WMD in overall hypoglycemia in patients with type 1 diabetes was -0.2 (95% CI, -1.1 to 0.7; P value not reported) for insulin analogs compared to REG. In patients with type 2 diabetes, the WMD was -0.2 (95% CI, -0.5 to 0.1; P=0.8). There were also no significant differences in overall hypoglycemia in pre-pubertal children. There were no statistically significant differences in these three groups. However, in the event rate of overall hypoglycemia in adolescents per patient per 30 days was significantly reduced with insulin analogs compared to REG (P=0.02). The event rate in pregnant women was significantly higher with insulin analogs compared to REG (P<0.05).<br><br>Secondary:<br>Overall, frequency and type of adverse events were comparable for the two treatment groups (P values not reported). |
| **Intermediate-Acting and Long-Acting Insulins: Type 1 Diabetes Mellitus** | | | | |
| Pieber et al.[56] (2007)<br><br>Insulin detemir BID (AM and HS) and insulin aspart before meals<br><br>vs<br><br>insulin glargine at bedtime and insulin aspart before meals<br><br>Insulin doses were titrated to achieve a target of | OL, PG, RCT<br><br>Men and women 18 years of age or older with type 1 diabetes for at least 1 year who had a BMI ≤35 $kg/m^2$ and $HbA_{1c}$ 7.5 to 12.0% | N=322<br><br>26 weeks | Primary:<br>Change in $HbA_{1c}$, change in FPG, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>At 26 weeks, both groups had comparable changes in $HbA_{1c}$ (between-treatment difference, -0.03; 95% CI, -0.25 to 0.19; P value not reported).<br><br>However, insulin glargine resulted in significantly lower home measured FPG than insulin detemir (7.0 vs 7.7 mmol/L, respectively; P<0.001).<br><br>The overall risk of hypoglycemia was comparable in both treatment groups (RR, 0.96; 95% CI, 0.68 to 1.35; P=0.811). However, insulin detemir resulted in lower rates of nocturnal hypoglycemia (episodes/subject-year) than with insulin glargine (4.3 vs 6.6, respectively; P<0.05).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| ≤7.3 mmol/L for pre-breakfast and pre-evening meal plasma glucose for insulin detemir and pre-breakfast plasma glucose for insulin glargine. | | | | |
| Heller et al.[57] (2009)<br><br>Insulin detemir PM or BID (AM and PM) and insulin aspart before meals<br><br>vs<br><br>insulin glargine PM and insulin aspart before meals<br><br>Basal insulin doses were titrated to achieve PG ≤108 mg/dL.<br><br>Prandial insulin doses were titrated to achieve PPG ≤162 mg/dL. | MC, NI, OL, PG, RCT<br><br>Patients ≥18 years of age with type 1 diabetes for ≥1 year who were receiving basal-bolus insulin regimen for ≥3 months with $HbA_{1c}$ ≤11.0% | N=443<br><br>52 weeks | Primary:<br>$HbA_{1c}$ at 52 weeks<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ ≤7.0% with or without major hypoglycemia in the last month of treatment, FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety | Primary:<br>Change in $HbA_{1c}$ from baseline at 52 weeks was -0.53 and -0.54% with insulin detemir and insulin glargine, respectively (mean difference, 0.01%; 95% CI, -0.13 to 0.16), confirming non-inferiority.<br><br>Patients receiving twice-daily insulin detemir experienced greater $HbA_{1c}$ reduction (-0.58%) compared to those receiving once-daily insulin detemir (-0.49%; P value not reported).<br><br>Secondary:<br>Similar percentage of patients achieved $HbA_{1c}$ ≤7.0% with insulin detemir compared to insulin glargine (33.0 vs 30.4%; P value not significant). The $HbA_{1c}$ goal was achieved without major hypoglycemia during the last month of treatment in 31.9 and 28.9% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS).<br><br>No significant differences were observed between the two groups with regard to changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles.<br><br>During the study, 91.6% of patients in the insulin detemir group and 88.2% in the insulin glargine group met the criteria to switch from once- to twice-daily dosing. At the end of the study, 65.8 and 4.8% of patients in the insulin detemir and insulin glargine groups, respectively, were receiving BID dosing. The total basal insulin dose at the end of the study was 0.40 units/kg and 0.33 units/kg with insulin detemir and insulin glargine, respectively. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | There were no significant differences between the two groups with regard to weight gain and incidence of hypoglycemia. Adverse events were reported in 92.6 and 89.6% of patients in the insulin detemir and insulin glargine groups, respectively. Twelve and one serious adverse events were probably or possibly related to insulin detemir and insulin glargine, respectively. Injection site reactions were reported more frequently with insulin detemir compared to insulin glargine (8.0 vs 1.4%; P value not reported). |
| Vague et al.[58] (2003)<br><br>Insulin detemir BID and insulin aspart before meals<br><br>vs<br><br>NPH insulin BID and insulin aspart before meals<br><br>Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL. | MC, OL, PG, RCT<br><br>Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥2 months; baseline $HbA_{1c}$ 8.18% for participants in the insulin detemir group and 8.11% for those randomized into the NPH group | N=448<br><br>26 weeks | Primary:<br>Effect on $HbA_{1c}$, FPG, variability in fasting self monitoring of blood glucose, weight gain, and frequency of hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>After six months, both insulin detemir and NPH reduced $HbA_{1c}$ -0.55% (P value NS).<br><br>After six months, FPG with insulin detemir (9.19 mmol/L) was comparable to NPH (9.94 mmol/L; P=0.097).<br><br>There was significantly less day-to-day fluctuation of fasting self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P<0.001).<br><br>Body weight change from baseline was significantly lower with insulin detemir (-0.2 kg) compared to NPH (0.7 kg; P<0.001).<br><br>The RR of hypoglycemia was 22% lower with insulin detemir compared to NPH (P<0.05). The RR of nocturnal hypoglycemia was 34% lower with insulin detemir compared to NPH (P<0.005).<br><br>Secondary:<br>Not reported |
| Hermansen et al.[59] (2004)<br><br>Insulin detemir BID and insulin aspart before meals | OL, RCT<br><br>Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥6 months, baseline $HbA_{1c}$ | N=595<br><br>18 weeks | Primary:<br>Effect on $HbA_{1c}$, FPG, self monitoring of blood glucose profile, weight gain, and frequency of | Primary:<br>After 18 weeks, $HbA_{1c}$ was significantly lower in the insulin detemir group (7.88%) compared to the NPH group (8.11%; P<0.001).<br><br>After 18 weeks, there was no significant difference in FPG with insulin detemir (7.58 mmol/L) compared to NPH (8.10 mmol/L; P>0.05).<br><br>There was significantly less day-to-day fluctuation of self monitoring of |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>NPH insulin BID and insulin aspart before meals | 8.48% for participants in the insulin detemir group and 8.29% for those randomized into the NPH group | | hypoglycemia<br><br>Secondary:<br>Not reported | blood glucose profiles with insulin detemir when compared to NPH (P<0.05).<br><br>Body weight change from baseline was significantly lower with insulin detemir (-0.95 kg) compared to NPH (0.07 kg; P<0.001).<br><br>The risk of hypoglycemia was 21% lower with insulin detemir compared to NPH (P=0.036). The risk of nocturnal hypoglycemia was 55% lower with insulin detemir compared to NPH (P<0.001).<br><br>Secondary:<br>Not reported |
| Home et al.[60] (2004)<br><br>Insulin detemir every morning (QAM) and at bedtime plus premeal insulin aspart<br><br>vs<br><br>insulin detemir every 12 hours (Q12H) plus premeal insulin aspart<br><br>vs<br><br>NPH insulin BID plus premeal insulin aspart | MC, OL, PG, RCT<br><br>Men and women >18 years of age with type 1 diabetes for >1 year already on mealtime plus basal insulin for >2 months, with a basal dose <100 IU/day, $HbA_{1c}$ ≤12.0%, BMI ≤35.5 kg/m$^2$ | N=409<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$, change in FPG from baseline<br><br>Secondary:<br>10-point self monitoring of blood glucose, frequency of hypoglycemia, weight gain | Primary:<br>At 16 weeks, there was no significant difference in $HbA_{1c}$ between all treatment groups (P=0.082). Insulin detemir every 12 hours had a reduction in $HbA_{1c}$ of -0.85%. When dosed every morning and at bedtime, $HbA_{1c}$ was reduced by -0.82%, whereas, NPH only reduced $HbA_{1c}$ by -0.65%. In combination, both detemir groups resulted in significantly greater reductions in $HbA_{1c}$ than NPH (difference, -0.18%; 95% CI, -0.34 to -0.02; P=0.027).<br><br>FPG levels were statistically significantly lower in both the detemir every 12 hours (P=0.004) and detemir every morning and at bedtime group (P<0.001) than the NPH group. Differences between the detemir groups did not result in statistical significance.<br><br>Secondary:<br>Overall 10-point self monitoring of blood glucose profiles were comparable between the three treatment groups (P>0.05).<br><br>The overall risk of hypoglycemia was significantly lower with insulin detemir every 12 hours (25%; P=0.046) and insulin detemir every morning and at bedtime (32%; P=0.002) compared to NPH. There were no significant differences in risk of nocturnal hypoglycemia between insulin detemir every 12 hours and NPH. However, when dosed every morning and at bedtime, insulin detemir had a significantly lower risk of nocturnal hypoglycemia than NPH (53%; P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Doses were titrated to achieve target FPG goals 4.0 to 7.0 mmol/L and PPG goals ≤10 mmol/L. | | | | Mean weight change was significantly decreased with insulin detemir every 12 hours (-0.8 kg; P=0.006) and insulin detemir every morning and at bedtime (-0.6 kg; P=0.040) when compared to NPH. However, there was no significant difference in weight change between the insulin detemir groups (P>0.05). |
| Russell-Jones et al.[61] (2004)<br><br>Insulin detemir HS and regular insulin before meals<br><br>vs<br><br>NPH insulin HS and regular insulin before meals<br><br>Doses were titrated to achieve target FPG goal 72 to 126 mg/dL and PPG goal of 180 mg/dL. | MC, OL, PG, RCT<br><br>Men and women ≥18 years of age with type 1 diabetes for ≥1 year already on basal or premixed insulin QD in the evening (5 PM to 11 PM) and REG before meals for ≥2 months and $HbA_{1c}$ ≤12.0% | N=749<br><br>6 months | Primary:<br>Change in $HbA_{1c}$ from baseline, change in FPG and fasting self monitoring of blood glucose, nine-point self monitoring of blood glucose profile, 24-hour continuous blood glucose monitoring, hypoglycemia, body weight<br><br>Secondary:<br>Not reported | Primary:<br>Mean $HbA_{1c}$ value decreased by -0.06% with insulin detemir while $HbA_{1c}$ increased by 0.06% with NPH. However, the baseline-adjusted mean $HbA_{1c}$ values did not significantly differ between groups (-0.12%; 95% CI, -0.25 to 0.02; P=0.083).<br><br>Both FPG and fasting self monitoring of blood glucose decreased similarly in the insulin detemir group and were slightly decreased with NPH. Both endpoints resulted in significant reductions with insulin detemir in comparison to NPH (P=0.001 and P<0.001, respectively).<br><br>Nine-point self monitoring of blood glucose profiles demonstrated significantly lower glucose values before breakfast with insulin detemir when compared to NPH (P<0.001).<br><br>In study participants that underwent 24-hour continuous blood glucose monitoring, insulin detemir had significantly less blood glucose fluctuations for mean levels nocturnally and over 24 hours (P<0.05).<br><br>Overall rates of hypoglycemia were comparable between groups. However, the RR of nocturnal hypoglycemia was 26% lower with insulin detemir compared to NPH (P=0.003). There was also a 30% risk reduction of minor hypoglycemic episodes during the night with insulin detemir (P=0.003).<br><br>Body weight gain was significantly lower with insulin detemir compared to NPH (-0.54 kg; P=0.024).<br><br>Secondary:<br>Not reported |
| Standl et al.[62] | ES, MC, OL, PG, | N=421 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (2004)<br><br>Insulin detemir BID and regular insulin before meals<br><br>vs<br><br>NPH insulin BID and regular insulin before meals<br><br>Basal insulin doses were adjusted to achieve FPG 4.0 to 7.0 mmol/L (72 to 126 mg/dL) and PPG <10 mmol/L (180 mg/dL). | RCT<br><br>Adult patients with type 1 diabetes on a basal-bolus insulin regimen for ≥2 months, baseline $HbA_{1c}$ 7.72% for participants taking insulin detemir and 7.66% for those randomized into the NPH group | (n=289 in the 6 month extension trial)<br><br>12 months (6-month treatment period and 6-month extension trial) | Effect on $HbA_{1c}$, FPG, nine-point self monitoring of blood glucose profile, weight gain, and frequency of hypoglycemia<br><br>Secondary:<br>Not reported | After 12 months, $HbA_{1c}$ was comparable between the insulin detemir group (7.88%) and the NPH group (7.78%; P=0.288).<br><br>After 12 months, there was no significant difference in FPG with insulin detemir (10.1 mmol/L) compared to NPH (9.84 mmol/L; P=0.665).<br><br>Mean nine-point self monitoring of blood glucose profiles showed significantly lower blood glucose 90-minutes after lunch and dinner (P<0.05). There were no significant differences at other times in the profile.<br><br>After 12 months, body weight change from baseline was significantly lower with insulin detemir (-1.44 kg) compared to NPH (0.3 kg; P<0.001).<br><br>There was no significant difference in the overall risk of hypoglycemia between insulin detemir and NPH (P=0.139). There was no significant difference in the risk of nocturnal hypoglycemia between insulin detemir and NPH (P=0.067).<br><br>Secondary:<br>Not reported |
| De Leeuw et al.[63] (2005)<br><br>Insulin detemir BID and insulin aspart before meals<br><br>vs<br><br>NPH insulin BID and insulin aspart before meals | ES, MC, OL, PG, RCT<br><br>Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥2 months, baseline $HbA_{1c}$ 8.18% for participants in the insulin detemir group and 8.03% for those | N=316<br><br>12 months (6-month treatment period and 6-month extension period) | Primary:<br>Effect on $HbA_{1c}$, FPG, nine-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain<br><br>Secondary:<br>Not reported | Primary:<br>Similar reductions in mean $HbA_{1c}$ values were observed in both treatment groups. After 12 months, insulin detemir reduced $HbA_{1c}$ -0.64% and NPH reduced $HbA_{1c}$ -0.56% (P value was not reported).<br><br>After 12 months, FPG with insulin detemir (10.7 mmol/L) was comparable to NPH (10.8 mmol/L; P value not reported).<br><br>Nine-point self monitoring of blood glucose profiles were comparable between insulin detemir when compared to NPH (value not reported; P<0.24).<br><br>There were no significant differences in overall rates of hypoglycemia between treatment groups. The RR of nocturnal hypoglycemia was 32% |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL. | randomized into the NPH group | | | lower with insulin detemir when compared to NPH (P=0.016).<br><br>After 12 months, body weight gain was significantly lower with insulin detemir compared to NPH (-1.34 kg; P<0.001).<br><br>Secondary:<br>Not reported |
| Pieber et al.[64] (2005)<br><br>Insulin detemir BID (AM and PM) and insulin aspart before meals<br><br>vs<br><br>insulin detemir BID (AM and HS) and insulin aspart before meals<br><br>vs<br><br>NPH insulin BID (AM and HS) and insulin aspart before meals<br><br>Basal insulin doses were adjusted to achieve FBG 72 to 126 mg/dL and PPG <180 mg/dL. | MC, OL, PG, RCT<br><br>Adult type 1 diabetes patients on a basal-bolus insulin regimen for ≥2 months; baseline $HbA_{1c}$ 8.01% for participants taking insulin detemir every morning and at dinner, 8.13% for those taking insulin detemir every morning and at bedtime, and 8.08% for those randomized into the NPH group | N=400<br><br>16 weeks | Primary:<br>Effect on $HbA_{1c}$ and FPG<br><br>Secondary:<br>Variability in fasting self monitoring of blood glucose, 10-point self monitoring of blood glucose, 24-hour glucose profile, frequency of hypoglycemia, and weight gain | Primary:<br>$HbA_{1c}$ was significantly reduced in all three groups. Insulin detemir dosed in the morning and at dinner reduced $HbA_{1c}$ -0.43%. When dosed in the morning and at bedtime, $HbA_{1c}$ was reduced -0.49%. NPH reduced $HbA_{1c}$ -0.39%. There was no significant difference between the groups (P=0.64).<br><br>FPG reductions were significantly greater with insulin detemir dosed in the morning and dinner (-0.17 mmol/L; P<0.001) and insulin detemir dosed in the morning and bedtime (-1.48 mmol/L; P<0.006) when compared to NPH (0.49 mmol/L). There was no significant difference in FPG between the insulin detemir groups (P=0.15).<br><br>Secondary:<br>Within-person variation in fasting self monitoring of blood glucose was significantly lower with either insulin detemir treatments compared to NPH (P<0.001). There was no significant difference in fasting self monitoring of blood glucose between the insulin detemir groups (P=0.48).<br><br>Overall 10-point self monitoring of blood glucose profiles were comparable between the three groups (P=0.103).<br><br>Twenty four-hour glucose profiles demonstrated lower glucose fluctuations with both insulin detemir treatments compared to NPH (P=0.049).<br><br>Overall and nocturnal rates of hypoglycemia were comparable between all groups. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Mean weight changes were significantly different with detemir dosed in the morning and dinner (-0.6 kg; P<0.001) and insulin detemir dosed in the morning and bedtime (0.1 kg; P=0.050) when compared to NPH (0.7 kg). |
| Kølendorf et al.[66] (2006)<br><br>Insulin detemir BID and insulin aspart before meals for 16 weeks<br><br>vs<br><br>NPH insulin BID and insulin aspart before meals for 16 weeks | OL, RCT, XO<br><br>Adult type 1 diabetes patients on a basal-bolus insulin regimen for >4 months, baseline $HbA_{1c}$ 7.9% for participants receiving insulin detemir first and 7.9% for those receiving NPH first | N=130<br><br>32 weeks | Primary:<br>Incidence of self-recorded hypoglycemia<br><br>Secondary:<br>Incidence of severe hypoglycemic episodes, effect on $HbA_{1c}$ and self monitoring plasma glucose | Primary:<br>The RR of hypoglycemia was 18% lower with insulin detemir compared to NPH (P=0.001). The RR of nocturnal hypoglycemia was 50% lower with insulin detemir compared to NPH (P<0.0001).<br><br>Secondary:<br>There were 19 severe hypoglycemic episodes with insulin detemir and 33 episodes with NPH; however, due to the low number of episodes an analysis could not be conducted.<br><br>$HbA_{1c}$ was reduced by approximately -0.3% in both treatment arms (P value was not reported).<br><br>There was significantly less day-to-day fluctuation of self-monitored plasma glucose profiles with insulin detemir when compared to NPH (P<0.001). |
| Robertson et al.[66] (2007)<br><br>Insulin detemir HS or BID (AM and HS) and insulin aspart before meals<br><br>vs<br><br>NPH insulin QD or BID and insulin aspart before meals<br><br>Insulin aspart | OL, PG, RCT<br><br>Children 6 to 17 years of age with type 1 diabetes, treated with insulin for at least 12 months (total daily dose ≤2 U/kg), and $HbA_{1c}$ ≤12.0% | N=347<br><br>26 weeks | Primary:<br>$HbA_{1c}$ and eight-point plasma glucose profiles assessed at 18 and 26 weeks, self-measured FPG on four days after 18 and 26 weeks<br><br>Secondary:<br>Hypoglycemia | Primary:<br>$HbA_{1c}$ at 26 weeks decreased by approximately -0.8% in both the insulin detemir and NPH groups (8.0 vs 7.9%, respectively; 95% CI, -0.1 to 0.3; P value not reported).<br><br>The mean eight-point plasma glucose profiles after 26 weeks were assumed parallel and did not have a statistically significant difference between insulin detemir and NPH (P=0.302). Plasma glucose levels were lower with insulin detemir than NPH at all time points except at 03.00 hour. However, the analysis of self-measured nocturnal plasma glucose at 03.00 hour did not show a statistical difference between treatments (P=0.194).<br><br>Mean self-measured FPG after 26 weeks was lower with insulin detemir than with NPH (P=0.022). Within-subject FPG variation also showed lower FPG levels with insulin detemir than NPH (P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| doses were titrated to achieve PPG 121 to 182 mg/dL. | | | | Secondary:<br>The study determined that the risk of having nocturnal hypoglycemia was 26% lower with insulin detemir (P=0.041). However, the risks of 24-hour and diurnal hypoglycemia were similar in both groups (P=0.351 and P=0.492, respectively). Also, the risks of having severe episodes, confirmed episodes or symptoms of hypoglycemia were similar in both groups (P=0.799, P=0.275, and P=0.425, respectively). |
| Bartley et al.[67] (2008)<br><br>Insulin detemir PM or BID and insulin aspart before meals<br><br>vs<br><br>NPH insulin PM or BID and insulin aspart before meals<br><br>Insulin doses were titrated to achieve plasma glucose target ≤6.0 mmol/l before breakfast and dinner. | OL, PG, RCT<br><br>Patients ≥18 years of age with type 1 diabetes, $HbA_{1c}$ ≤11.0%, BMI ≤35.0 kg/m$^2$, and receiving a basal-bolus insulin regimen ≥3 months | N=497<br><br>24 months | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, proportion of patients achieving $HbA_{1c}$ ≤7.0% without hypoglycemia, incidence in hypoglycemia, change in baseline body weight, safety | Primary:<br>Insulin detemir resulted in significantly greater decreases in $HbA_{1c}$ compared to NPH (final $HbA_{1c}$, 7.36 vs 7.50%; decrease, -0.94 vs -0.72%; difference, -0.22%; 95% CI, -0.41 to -0.03).<br><br>Secondary:<br>Insulin detemir significantly decreased FPG compared to NPH (final FPG, 8.35 vs 9.43 mmol/L; P=0.019).<br><br>Significantly more patients receiving insulin detemir achieved $HbA_{1c}$ ≤7.0% without hypoglycemia compared to patients receiving NPH (22 vs 13%; P=0.019).<br><br>The risk of major and nocturnal hypoglycemia was significantly lower with insulin detemir (P<0.001). Specifically, insulin detemir was associated with a 69 and 49% lower risk of major and nocturnal hypoglycemia.<br><br>Insulin detemir resulted in significantly less weight gain compared to NPH (1.7 vs 2.7 kg; P=0.024).<br><br>The overall safety prolife was similar between the two treatments. Four deaths were reported with insulin detemir (cardiorespiratory arrest in relation to status epilepticus, sudden death, bronchopneumonia, and MI following surgery). All events were judged to not be related to insulin detemir. Withdrawals due to adverse events were more common with insulin detemir. |
| Ratner et al.[68] (2000) | PG, RCT<br><br>Type 1 diabetes | N=534<br><br>28 weeks | Primary:<br>Effect on $HbA_{1c}$, FPG, and | Primary:<br>Reduction in $HbA_{1c}$ was similar with NPH (-0.21%) and insulin glargine (-0.16%; P=0.4408). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Insulin glargine HS<br><br>vs<br><br>NPH insulin HS or BID (AM and HS)<br><br>Doses of both insulins were titrated to achieve preprandial blood glucose 4.4 to 6.7 mmol/L. | patients, baseline $HbA_{1c}$ 7.7% in both groups | | incidence of hypoglycemia<br><br>Secondary:<br>Not reported | Reduction in FPG was similar with NPH (-0.94 mmol/L) and insulin glargine (-1.12 mmol/L; P=0.3546).<br><br>After the one month titration phase, significantly less patients on insulin glargine reported symptomatic hypoglycemia (39.9 vs 49.2%; P=0.0219) or nocturnal hypoglycemia (18.2 vs 27.1%; P=0.0116).<br><br>Overall incidence of all symptomatic hypoglycemia was similar between treatment groups throughout the study.<br><br>Secondary:<br>Not reported |
| Tan et al.[69] (2004)<br><br>Analysis was on data 6 months prior to initiating insulin glargine therapy and data 6 months after initiating insulin glargine therapy.<br><br>Patients were divided into those taking insulin glargine only and those taking insulin glargine plus NPH insulin in the AM. | RETRO<br><br>Patients ≤18 years of age with type 1 diabetes when initiating insulin glargine therapy between June 1, 2001 and June 30, 2002, not using continuous SC insulin infusion or inhaled insulin before starting insulin glargine therapy | N=71<br><br>12 months | Primary:<br>Change in $HbA_{1c}$, blood glucose concentrations, hypoglycemia (number of self-reported symptomatic hypoglycemia and number of blood glucose readings <50 mg/dL)<br><br>Secondary:<br>Not reported | Primary:<br>There was no difference in $HbA_{1c}$ between baseline and six months after initiating insulin glargine therapy (8.9±1.6% and 8.9±1.5%, respectively). In the divided groups, there was no statistical difference in the change in $HbA_{1c}$ between patients taking insulin glargine only vs patients taking insulin glargine plus NPH (P value not reported).<br><br>Mean blood glucose concentrations decreased slightly after initiating insulin glargine in all subjects. Patients taking insulin glargine plus NPH had slight improvements in average blood glucose levels, whereas patients taking insulin glargine only had a slight deterioration and a slight rise in average blood glucose levels. All changes were not statistically significant (P values not reported).<br><br>There was a decrease in self-reported episodes of symptomatic hypoglycemia after initiating insulin glargine therapy. However, there was no difference between baseline and after starting insulin glargine therapy in the frequency of blood glucose values <50 mg/dL (P value not reported).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Ashwell et al.[70] (2006)<br><br>Insulin glargine HS and insulin lispro before meals for 16 weeks<br><br>vs<br><br>NPH insulin QD or BID and regular insulin before meals for 16 weeks<br><br>Doses were adjusted to achieve target pre-breakfast, preprandial, and postprandial levels of 4.0 to 6.5 mmol/L, in the absence of hypoglycemia. | MC, RCT, 2-way, XO<br><br>Patients aged 18 to 65 years of age with type 1 diabetes, no previous experience with insulin glargine, previously on a multiple insulin injection regimen for at least 1 year, random C-peptide ≤0.10 nmol/L, $HbA_{1c}$ 7.0 to 9.5% | N=56<br><br>32 weeks | Primary:<br>$HbA_{1c}$ at treatment endpoints<br><br>Secondary:<br>Prebreakfast self monitoring of blood glucose concentration, 24-hour eight-point self monitoring of blood glucose levels, 24-hour inpatient plasma glucose levels, monthly rate of hypoglycemia | Primary:<br>At 16 weeks, $HbA_{1c}$ was lower with insulin glargine compared to NPH (between treatment difference, -0.5; 95% CI, -0.7 to -0.3; P<0.001).<br><br>Secondary:<br>Prebreakfast self monitoring of blood glucose concentration was lower in the insulin glargine group than the NPH group (between treatment difference, -1.5; 95% CI, -2.6 to -0.5; P<0.005).<br><br>Self monitoring of blood glucose concentrations were lower before and after breakfast with insulin glargine compared to NPH. The 24-hour eight-point self monitoring of blood glucose concentrations was also lower with insulin glargine (between treatment difference, -1.9; 95% CI, -3.1 to -0.8; P=0.001).<br><br>During the inpatient assessment, 24-hour eight-point self monitoring of blood glucose levels were lower at all points with insulin glargine compared to NPH (P=0.037 for plasma glucose AUC; P=0.002 for PPG AUC; P=0.038 for plasma glucose before breakfast).<br><br>Seventy-two percent of patients taking insulin glargine reported nocturnal hypoglycemia compared to 83% of patients taking NPH. This resulted in a -44% reduction in the monthly rate of nocturnal hypoglycemia with insulin glargine compared to NPH (P<0.001). |
| Herwig et al.[71] (2007)<br><br>Insulin glargine QD and regular insulin or insulin lispro before meals<br><br>vs<br><br>NPH insulin QD to TID and regular insulin or insulin | OL<br><br>Pediatric patients with type 1 diabetes for >1 year duration | N=142<br><br>20±10 months | Primary:<br>$HbA_{1c}$, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>$HbA_{1c}$ significantly increased from 7.3±1.0% to 7.6±1.1% (P=0.003) and from 7.7±1.6% to 8.3±1.5% (P=0.0001) in both the insulin glargine and NPH groups.<br><br>The incidence of symptomatic hypoglycemia was comparable between both groups; however, the overall incidence of severe hypoglycemia was significantly lower in the insulin glargine group (P=0.002).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| lispro before meals<br><br>Doses of insulin glargine were titrated to achieve target FBG 4.4 to 7.8 mmol/L and doses of NPH insulin were titrated to achieve target FBG 4.4 to 8.9 mmol/L. | | | | |
| Kudva et al.[72] (2007)<br><br>Insulin glargine and insulin aspart before meals<br><br>vs<br><br>ultralente insulin and insulin aspart before meals | RCT, XO<br><br>Patients with median age of 43 years with type 1 diabetes | N=22<br><br>16 weeks | Primary:<br>Hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>Measures of glycemic variation did not differ significantly between insulin glargine and ultralente insulin. In the insulin glargine group, the standard deviation of blood glucose showed a tendency to be lower and the standard deviation of nocturnal blood glucose concentrations was significantly lower. However, glucose concentrations were significantly lower during the one hour before and three hours after lunch with ultralente insulin.<br><br>Secondary:<br>Not reported |
| Chatterjee et al.[73] (2007)<br><br>Insulin glargine QD and insulin aspart before meals for 16 weeks<br><br>vs<br><br>NPH insulin BID and insulin aspart before meals for 16 | OL, RCT, XO<br><br>Patients 18 to 75 years of age with type 1 diabetes for at least 6 months on either BID or multiple dose insulin injections, BMI <45 kg/m$^2$, $HbA_{1c}$ 6.0 to 11.0% | N=60<br><br>36 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Frequency of overall hypoglycemic episodes, change in FPG, body weight, lipid profile | Primary:<br>At 36 weeks, treatment with insulin glargine resulted in lower $HbA_{1c}$ levels compared to NPH (between-treatment difference, -0.19±0.09; 95% CI, -0.36 to 0.01; P=0.04). At the end of the second treatment period, those patients switching from glargine to NPH experienced an increase in $HbA_{1c}$ of 0.16%, whereas those who switched from NPH to glargine experienced a reduction of -0.1%.<br><br>Secondary:<br>Both groups had similar mean incidences of overall hypoglycemic episodes (between-treatment difference, 1.21; 95% CI, 0.56 to 2.64; P=0.63). The OR for the incidence of hypoglycemia compared in both groups was 1.2 (95% CI, 0.55 to 2.59; P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| weeks | | | | FPG was also lower with insulin glargine vs NPH (between-treatment difference, -3.00; 95% CI, -4.80 to -1.20; P<0.01).<br><br>There was no significant difference in change in body weight between both groups (mean difference, -0.24; 95% CI, -0.87 to 0.39; P=0.45). Similarly, there was no difference in TC or TG levels between groups (P value not reported). |
| Manini et al.[74] (2007)<br><br>Insulin glargine<br><br>vs<br><br>intensive insulin treatment (NPH) | RCT<br><br>Patients with a mean age of 46 years with type 1 diabetes for at least 1 year duration and suboptimal glucose control under intensive insulin treatment | N=47<br><br>8 months | Primary:<br>Change in $HbA_{1c}$, health-related quality of life<br><br>Secondary:<br>Not reported | Primary:<br>Insulin glargine resulted in a mean $HbA_{1c}$ decrease of -0.7% from baseline (P<0.0001).<br><br>Insulin glargine also resulted in improved health-related quality of life scores using a Well-being Enquiry for Diabetics questionnaire. The results showed improvements in discomfort (P=0.020), impact (P=0.0002), and total score (P=0.0005). The questionnaire score changes were also associated with a lower perceived risk of hypoglycemia and fewer daily-life associated issues with insulin glargine.<br><br>Secondary:<br>Not reported |
| Rosenstock et al.[75] (2000)<br><br>Insulin glargine HS (containing 30 µg/mL zinc chloride)<br><br>vs<br><br>insulin glargine HS (containing 80 µg/mL zinc chloride)<br><br>vs | DB, MC, PG, RCT<br><br>Patients with type 1 diabetes on basal-bolus multiple daily insulin regimen for at least 2 months, 18 to 70 years of age, had BMI 18 to 28 $kg/m^2$, $HbA_{1c}$ <10.0%, postprandial serum C-peptide <0.2 pmol/mL | N=256<br><br>4 weeks | Primary:<br>FPG at study end point calculated as the mean of three FPG values on days 27, 28 and 29<br><br>Secondary:<br>Change from baseline in overnight plasma glucose, mean FPG, blood glucose profile, nocturnal blood glucose, stability | Primary:<br>Adjusted mean FPG at end point was 9.2 mmol/L for the pooled insulin glargine groups and 11.3 mmol/L for the NPH group (P=0.001).<br><br>Secondary:<br>The adjusted mean overnight plasma glucose levels after 5 AM were 7.8 mmol/L for insulin glargine 30, 7.3 mmol/L for insulin glargine 80, and 10.7 mmol/L for NPH (P values not reported).<br><br>At the end of the study, the mean standard deviations for FPG were 7.6±2.3 and 7.5±1.9 mmol/L for the insulin glargine 30 and insulin glargine 80 groups, respectively, and 9.0±2.4 mmol/L for the NPH group (P<0.001).<br><br>Blood glucose profile determined from seven self monitoring of blood glucose values during the day was not different among the treatment group |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| NPH insulin HS or BID | | | of FPG, $HbA_{1c}$, safety and adverse events | (P value not reported).<br><br>Nocturnal blood glucose measured by self monitoring of blood glucose at 3 AM was higher in the insulin glargine group than in the NPH group (P value not reported).<br><br>Stability of FPG was significantly lower in patients receiving insulin glargine 30 compared to patients receiving NPH (P<0.05).<br><br>The mean standard deviation for $HbA_{1c}$ levels were -0.40±0.48 and -0.40±-0.49 in the insulin glargine 30 and insulin glargine 80 groups, respectively, and -0.40±0.48 in the NPH group (P value not reported).<br><br>Fewer patients receiving NPH (93.2%) reported a hypoglycemic episode than patients receiving insulin glargine (97.6 and 100% for insulin glargine 30 and insulin glargine 80, respectively; P=0.03). All events were considered mild and none resulted in discontinuation from study treatment.<br><br>Insulin glargine was as safe as NPH with no differences between treatments with regard to the incidence of adverse effects, including the most frequent event, injection site reactions. |
| Rossetti et al.[76] (2003)<br><br>Insulin glargine PM and insulin lispro before meals<br><br>vs<br><br>insulin glargine HS and insulin lispro before meals<br><br>vs | RCT<br><br>Patients with type 1 diabetes and fasting plasma C-peptide ≤0.15 nmol/L on intensified treatment with multiple daily combinations of lispro and NPH at each meal and NPH at bedtime | N=51<br><br>12 weeks | Primary:<br>$HbA_{1c}$ level<br><br>Secondary:<br>Blood glucose profile from home blood glucose monitoring, hypoglycemia | Primary:<br>In patients taking NPH, $HbA_{1c}$ increased slightly from baseline, but was not statistically significant. However, $HbA_{1c}$ decreased both with the dinnertime as well as the bedtime dose of insulin glargine (P<0.04). There was no significant difference in the change of $HbA_{1c}$ in both insulin glargine groups (P value NS).<br><br>Secondary:<br>Patients taking insulin glargine had lower blood glucose concentrations in the fasting state, after breakfast, before lunch, and after lunch (P<0.05). The before-dinner blood glucose with NPH and insulin glargine at dinnertime was similar (P value NS), but was lower with insulin glargine at bedtime (P<0.05). The after-dinner blood glucose was lower with insulin glargine at dinner-time and bedtime than with NPH (P<0.05). However, the bedtime blood glucose was not different with all three |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| NPH insulin QD and insulin lispro before meals<br><br>Glycemic targets were blood glucose 6.4 to 7.2 mmol/L in the fasting state, before meals, and at bedtime and blood glucose at 8.0 to 9.2 mmol/L 90 minutes after meals. | | | | treatment groups (P value NS).<br><br>The frequency of mild hypoglycemia was lower in patients taking insulin glargine than in patients taking NPH (P<0.005). There was no difference between the insulin glargine at dinnertime and insulin glargine at bedtime groups (P value NS). Patients taking insulin glargine had a lower frequency of nocturnal hypoglycemic episodes than patients taking NPH (P<0.05). There were no differences between both insulin glargine groups (P value NS). |
| Pesić et al.[77] (2007)<br><br>Insulin glargine QD and insulin aspart before meals<br><br>vs<br><br>NPH insulin HS and insulin aspart before meals<br><br>vs<br><br>NPH insulin BID and insulin aspart before meals | RCT<br><br>Patients with type 1 diabetes on long-term conventional insulin therapy | N=48<br><br>12 weeks | Primary:<br>Change in FPG, change in $HbA_{1c}$<br><br>Secondary:<br>Frequency of hypoglycemia | Primary:<br>FPG was lower in the glargine group in comparison to the NPH BID group (7.30 vs 7.47 mmol/L, respectively), but this difference was not significant. FPG levels for the NPH-at-bedtime group were reported as significantly higher compared to either of the other two groups (8.44 mmol/L; P<0.05).<br><br>At 12 weeks, $HbA_{1c}$ decreased in both the NPH BID (from 7.80±0.83% to 7.01±0.63%) and insulin glargine groups (from 7.72±0.86% to 6.87±0.50%). However, there was no change in $HbA_{1c}$ in the NPH-at-bedtime group.<br><br>Secondary:<br>A lower frequency of mild hypoglycemic episodes was observed in the insulin glargine group compared to both NPH groups (P<0.05). |
| Dundar et al.[78] (2009)<br><br>NPH QD<br><br>vs | RETRO, XO<br><br>Pediatric and adolescent patients with a mean age of 12.7±3.4 years, | N=34<br><br>12 months (6 months of NPH, followed | Primary:<br>Mean total daily insulin dose, mean FPG, numbers of severe and | Primary:<br>Total daily insulin doses were similar among all three insulin groups (P>0.05 for all comparisons).<br><br>No significant difference was seen in mean FPG between NPH and both long-acting insulins combined (P>0.05). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| insulin detemir QD<br><br>vs<br><br>insulin glargine QD<br><br>All patients received NPH insulin for ≥6 months before transitioning to either insulin detemir or insulin glargine at a dose that was 40 to 45% of total daily NPH insulin dose, in addition to insulin aspart TID at the same doses. | with type 1 diabetes for 5.4±3.0 years who were receiving NPH insulin daily and insulin aspart three times daily for ≥6 months | by 6 months of insulin detemir or insulin glargine) | nocturnal hypoglycemia, mean $HbA_{1c}$, BMI SDS and safety<br><br>Secondary:<br>Not reported | Incidence of severe hypoglycemia with NPH was similar compared to insulin detemir and insulin glargine (P>0.05).<br><br>Eight episodes of nocturnal hypoglycemia was reported in four patients during NPH treatment compared to three episodes reported in three patients in both long-acting insulin groups combined (P>0.05).<br><br>Mean $HbA_{1c}$ was significantly lower with insulin glargine and insulin detemir compared to NPH (P<0.05 for both). No significant difference was seen between insulin glargine and insulin detemir.<br><br>The increase in BMI SDS was significantly lower with insulin detemir compared to the increase seen with NPH and insulin glargine (P<0.05 for both). No difference was noted between NPH and insulin glargine.<br><br>No adverse events were reported during treatment with insulin glargine and insulin detemir.<br><br>Secondary:<br>Not reported |
| Chase et al.[79] (2008)<br><br>Insulin glargine AM and insulin lispro before meals<br><br>vs<br><br>NPH or Lente insulin BID (AM and PM) and insulin lispro before meals | AC, OL, PG, RCT<br><br>Patients 9 to 17 years of age with type 1 diabetes with $HbA_{1c}$ ≥7.0 to ≤9.5%, and receiving any daily insulin regimen consisting of ≥2 injections or a continuous infusion | N=175<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Incidence of hypoglycemia, safety | Primary:<br>There was no difference in the decrease in $HbA_{1c}$ with insulin glargine (-0.25%) and NHP (0.05%; P=0.1725). However, it was reported that the decrease in $HbA_{1c}$ was significantly greater with insulin glargine in patients with higher baseline $HbA_{1c}$.<br><br>Secondary:<br>The incidence of hypoglycemia was significantly higher with insulin glargine (P=0.0298). There was no difference in the incidence of severe hypoglycemia between the two treatments.<br><br>Both treatments were well tolerated and there was no difference in the rate of overall adverse events between them (P=0.1944). Metabolism and |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Basal insulin doses were titrated to achieve FPG 70 to 100 mg/dL. | | | | nutrition disorders (e.g., hypoglycemia, hyperglycemia, etc) were the most commonly reported treatment-emergent adverse events, and these occurred with comparable frequency between the two treatments (11.8 vs 5.6%; P=0.1803). Significantly more serious adverse events were reported with insulin glargine (P=0.0164). |
| Ahern et al.[80] (2002)<br><br>Insulin pump therapy containing basal insulin<br><br>The total patient population was stratified based on age: 1 to 6 years, 7 to 11 years, and 12 to 18 years.<br><br>Patients were started on daily dose of insulin therapy prior to study start.<br><br>The total daily dose was divided as 50% premeal bolus doses and 50% as basal replacement, given as a single hourly rate over the first 24 hours. | PRO<br><br>Patients ≤18 years of age with type 1 diabetes, followed in children's diabetes clinic for at least 1 year prior to start of pump therapy, previously on a 2 to 3 injection/day regimen | N=161<br><br>Average of 32±9 months | Primary:<br>$HbA_{1c}$, diabetes-related adverse events<br><br>Secondary:<br>Not reported | Primary:<br>Patients in all three groups had good diabetes control prior to study start. However, $HbA_{1c}$ levels fell by 0.6 to 0.7% in all three groups by 12 months. These levels were significantly lower than prepump levels (P≤0.02).<br><br>Within each age group, the incidence of severe hypoglycemic events during pump therapy was lower than during prior injection therapy. The differences did not achieve statistical significant.<br><br>When all three groups were combined, there was a significantly lower incidence of severe hypoglycemic events during the first 12 months of pump therapy than during the 12 months prior to pump therapy (P<0.05).<br><br>Secondary:<br>Not reported |
| **Intermediate-Acting and Long-Acting Insulins: Type 2 Diabetes Mellitus** | | | | |
| Meneghini et al.[81] (2007) | OL, OS | N=1,832 | Primary:<br>Incidence of severe | Primary:<br>No severe adverse drug reactions were reported during the 12 week |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Insulin detemir±oral antidiabetic drug transferred from 3 groups of patients: oral antidiabetic drug only, NPH±oral antidiabetic drug, insulin glargine±oral antidiabetic drug | Subgroup of patients with type 2 diabetes from the German cohort of PREDICTIVE study | 12 weeks | adverse drug reactions (severe adverse drug reactions) (major hypoglycemic events)<br><br>Secondary: Hypoglycemic events, weight changes, $HbA_{1c}$, FPG | follow-up. Reports of adverse drug reactions occurred in 0.3% of patients, including one report of drug intolerance, two diabetes-related reports, one report of headache, and one report of skin allergy (P values were not reported).<br><br>Secondary:<br>The percentage of patients experiencing hypoglycemia and the frequency of hypoglycemic episodes were lower in the insulin detemir group during the four weeks preceding the follow-up visit compared to baseline. The total, daytime, and nocturnal hypoglycemic events at baseline decreased from 3.3, 2.0, and 1.3 events/patient-year, respectively, to -2.7, -1.6, and -1.2, respectively (P<0.0001). The percentage of patients experiencing these events decreased from 7.2, 5.5, and 3.7%, respectively, to 2.0, 1.6, and 0.5% at follow-up (P values not reported).<br><br>There were overall reductions in body weight following the transition to insulin detemir (P<0.0001). All three groups of patients had weight reduction after initiating insulin detemir (P<0.0001 in the oral antidiabetic drug only group, P<0.0099 in the NPH±oral antidiabetic drug group, and P<0.0001 in the insulin glargine±oral antidiabetic drug group).<br><br>A reduction of -1.1±0.03% in mean $HbA_{1c}$ was observed at study endpoint (P<0.0001). Patients that were in the oral antidiabetic drug only group had a reduction of -1.29±0.03% (P<0.0001) from baseline, which was a slightly greater reduction than in the NPH±oral antidiabetic drug and insulin glargine±oral antidiabetic drug groups (-0.60±0.09% and -0.59±0.06%, respectively; P<0.0001 for both).<br><br>There was a significant reduction in mean FPG overall (P<0.0001). However, patients transitioning from the oral antidiabetic drug only group tended to have a greater reduction in FPG from baseline than those transitioning from the other two treatment regimens (P<0.0001). |
| Hollander et al.[82] (2008)<br><br>Insulin detemir PM or BID (AM and | MC, NI, OL, PG, RCT<br><br>Patients ≥18 years of age with type 2 | N=319<br><br>52 weeks | Primary: $HbA_{1c}$ at 52 weeks<br><br>Secondary: | Primary:<br>Mean $HbA_{1c}$ at 52 weeks was 7.19% with insulin detemir and 7.03% with insulin glargine (mean difference, 0.17; 95% CI, -0.07 to 0.40), meeting the prespecified non-inferiority margin. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| PM) and insulin aspart before meals<br><br>vs<br><br>insulin glargine PM and insulin aspart before meals<br><br>Basal insulin doses were titrated to achieve pre-breakfast and pre-dinner PG ≤108 mg/dL.<br><br>Prandial insulin doses were titrated to achieve PPG ≤162 mg/dL.<br><br>Insulin secretagogues and α-glucosidase inhibitors were discontinued.<br><br>United States patients on TZDs were allowed to continue treatment. | diabetes for ≥1 year who were receiving oral diabetic medications or insulin with or without oral diabetes medications for >4 months with $HbA_{1c}$ 7.0 to 11.0% and BMI ≤40 kg/m$^2$ | | Change in body weight, proportion of patients achieving $HbA_{1c}$ ≤7.0% with or without major hypoglycemia in the last three months of treatment, FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose, 10-point self-monitored plasma glucose profiles and safety | Secondary:<br>Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (2.8 vs 3.8 kg; P<0.05).<br><br>Similar percentage of patients achieved $HbA_{1c}$ ≤7.0% with insulin detemir compared to insulin glargine (36.2 vs 36.7%; P value NS). The $HbA_{1c}$ goal was achieved without symptomatic hypoglycemia in 17.1 and 21.4% of patients in the insulin detemir and insulin glargine groups, respectively (P value NS).<br><br>No significant differences were observed between the two groups with regard to FPG at the end of study, changes in FPG, within-patient variation in self-monitored pre-breakfast and pre-dinner blood glucose and 10-point self-monitored plasma glucose profiles.<br><br>Episodes of major hypoglycemia were reported in 4.7 and 5.7% of patients in the insulin detemir and insulin glargine groups, respectively (P=0.588). Incidence of nocturnal and symptomatic hypoglycemia was also comparable between the two groups (P>0.05 for both).<br><br>Severe treatment-emergent adverse events were reported in 13.6 and 19.0% of patients in the insulin detemir and insulin glargine groups. |
| Raskin et al.[83] (2009)<br><br>Insulin detemir PM or BID (AM and PM) and insulin | MC, NI, OL, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes who | N=385<br><br>26 weeks | Primary:<br>$HbA_{1c}$ at 26 weeks<br><br>Secondary:<br>FPG, body weight, | Primary:<br>The least squared mean change in $HbA_{1c}$ from baseline at 26 weeks was -1.08% with insulin detemir and -1.28% with insulin glargine (difference, 0.207; 95% CI, 0.0149 to 0.3995; P=0.035), showing non-inferiority. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| aspart before meals (IDet)<br><br>vs<br><br>insulin glargine PM and insulin aspart before meals (IGla)<br><br>Basal insulin doses were titrated to achieve pre-breakfast PG ≤108 mg/dL.<br><br>Treatment with insulin secretagogues and α-glucosidase inhibitors were discontinued.<br><br>Treatment with TZDs and metformin was continued. | previously received any oral diabetes medication or insulin with or without oral diabetes medications with $HbA_{1c}$ 7.0 to 11.0% and BMI ≤40 kg/m$^2$ | | safety | When last observation carried forward analysis was used, the least squared mean change in $HbA_{1c}$ was -0.94 and -1.25% with insulin detemir and insulin glargine, respectively. The difference between the two groups (0.307; 95% CI, 0.1023 to 0.5109; P=0.004) was inconclusive regarding possible inferiority of insulin detemir since the 95% CI included 0.4, the prespecified inferiority margin.<br><br>Secondary:<br>No significant differences were seen in change in FPG from baseline at 26 weeks between the two treatment groups.<br><br>Patients in the insulin detemir group experienced less weight gain compared to those in the insulin glargine group (1.20±3.96 vs 2.70±3.94 kg; P=0.001).<br><br>Rates of overall, nocturnal and major hypoglycemic events were comparable between the two groups. Sixty-six percent of patients in the insulin detemir group and 71% in the insulin glargine group reported treatment-emergent adverse events. |
| Rosenstock et al.[84] (2008)<br><br>Insulin detemir PM or BID (AM and HS)<br><br>vs<br><br>insulin glargine HS | MC, NI, OL, PG, RCT<br><br>Insulin-naïve type 2 diabetics ≥18 years of age, receiving oral antidiabetic agents, with $HbA_{1c}$ 7.5 to 10.0%, and BMI ≤40.0 kg/m$^2$ | N=582<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline plasma glucose and body weight, proportion of patients achieving $HbA_{1c}$ ≤7.0% | Primary:<br>Decreases in $HbA_{1c}$ were -1.5% with both treatments and were comparable after 52 weeks at 7.2 and 7.1% (difference, 0.05%; 95% CI, -0.11 to 0.21), thereby meeting the criteria for non-inferiority for insulin detemir vs insulin glargine.<br><br>Secondary:<br>Within-patient variation of self-monitored plasma glucose pre-breakfast and -dinner did not differ significantly between the two treatments. The overall shape of the 10-point self-monitored plasma glucose profile during the last week of treatment was similar between the two treatments |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Basal insulin doses were titrated to achieve FPG ≤6 mmol/L.<br><br>Existing oral antidiabetic drug therapy was continued. | | | without hypoglycemia, incidence of hypoglycemia, safety | (P value NS).<br><br>Weight gain was significantly less with insulin detemir compared to insulin glargine (3.0 vs 3.9 kg; P=0.01).<br><br>With both treatments, 52% of patients achieved $HbA_{1c}$ ≤7.0%, with 33 and 35% of patients receiving insulin detemir and insulin glargine doing so without hypoglycemia (P value not reported).<br><br>The risk of hypoglycemia of any type was comparable between the two treatments. The overall rate was low at 5.8 vs 6.2 episodes per patient-year with insulin detemir vs insulin glargine (RR, 0.94; 95% CI, 0.71 to 1.25), while the rate of nocturnal hypoglycemia was 1.3 episodes per patient-year with both treatments.<br><br>Serious adverse events were less frequent with insulin detemir (42 patients with 47 events vs 53 patients with 73 events; P value not reported). One death was reported with insulin detemir (cause and/or reason unknown). Adverse events recorded as serious tended to be of a wide-ranging disparate nature, with no clear pattern of between-treatment differences. The only differences in adverse events were injection-site disorders (4.5 vs 1.4%), allergic reactions (3 vs 1 patients), and skin disorders including pruritis and rash (6 vs 1 patients). |
| King.[85] (2009)<br><br>Insulin detemir SC QD<br><br>vs<br><br>insulin glargine SC QD<br><br>Once the patient achieved 2 consecutive days at | DB, RCT, XO<br><br>Type 2 diabetics receiving oral antidiabetic agents | N=36<br><br>24 hours | Primary:<br>24-hour glycemic control, time to basal glycemic control, insulin dose<br><br>Secondary:<br>Not reported | Primary:<br>Glucose profiles for each hour were similar between the two treatments. Glucose values for each five minute interval for insulin detemir during the basal period, the period 12 hours after injection, and overall 24-hour period were similar to insulin glargine.<br><br>The AUC for the self-monitored glucose levels over 24 hours was 293.2 and 3,114.5 mg.h/dL (point ratio, 0.941; 90% CI, 0.885 to 1.001); therefore, the two treatments were considered bioequivalent for 24-hour glucose.<br><br>Target basal glycemic control was achieved in all patients in 3.8 and 3.5 days with insulin detemir and insulin glargine (*P*=0.360). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| goal, the insulin treatment was switched to the other agent. | | | | The dose of insulin detemir was similar to that of insulin glargine (26.3 and 22.6 units/day; *P*=0.837). Approximately one percent of all glucose values during the basal period were <70 mg/dL.<br><br>Secondary:<br>Not reported |
| Liebl et al.[86] (2009)<br><br>Insulin detemir PM and insulin aspart before meals<br><br>vs<br><br>biphasic insulin aspart 30 (consisting of 30% insulin aspart and 70% protamine-crystallized insulin aspart) BID<br><br>Insulin detemir doses were titrated to achieve pre-breakfast PG 72 to 126 mg/dL and insulin aspart doses were titrated to achieve PPG ≤180 mg/dL.<br><br>Biphasic insulin aspart doses were titrated to achieve pre-breakfast and | MC, RCT<br><br>Adult type 2 diabetics ≥6 months, BMI ≤40 kg/m$^2$, currently receiving 1 or 2 oral antidiabetic agents, with or without concomitant QD intermediate- or long-acting insulin, and $HbA_{1c}$ ≥7.0 to ≤12.0% | N=719<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ ≤7.0%; change in baseline FPG and body weight, self-monitored glucose prolife, incidence of hypoglycemia | Primary:<br>Insulin detemir plus insulin aspart significantly decreased $HbA_{1c}$ compared to biphasic aspart 30 (-1.56 vs -1.23%; treatment difference, 0.234%; 95% CI, 0.398 to -0.070; P=0.0052). Final $HbA_{1c}$ values were 6.96 and 7.17%.<br><br>Secondary:<br>After 26 weeks, 60 and 50% of patients achieved $HbA_{1c}$ ≤7.0% with insulin detemir plus insulin aspart and biphasic aspart 30 (P value not reported). Patients previously receiving basal insulin had significantly greater decrease with insulin detemir plus insulin aspart (-1.21 vs -0.75%; P=0.0129), whereas insulin-naïve patients had similar decreases (-1.69 vs -1.42%; P=0.106).<br><br>There was no difference in the decrease of FPG between the two treatments (-52.3 vs -51.8 mg/dL; P=0.345).<br><br>There was no difference in the amount of weight gain between the two treatments (4.1 vs 4.0 kg; P value not reported).<br><br>Daily glucose profiles indicate that both treatments decrease glucose levels throughout the day. PPG was significantly lower with insulin detemir plus insulin aspart compared to biphasic aspart 30 (after breakfast; P=0.012, after lunch; P<0.001, and after dinner; P<0.001).<br><br>A total of five and zero patients experienced major hypoglycemia with insulin detemir plus insulin aspart compared to biphasic aspart 30 (P value not reported). The rate of minor hypoglycemia was 31 vs 28%; P=0.837). The rate of nocturnal minor hypoglycemia was similar between the two treatments (7.4 vs 7.3%; P=0.666). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| pre-dinner plasma glucose 72 to 126 mg/dL.<br><br>All oral antidiabetic drugs were discontinued to compare two insulin regimens. | | | | |
| Haak et al.[87] (2005)<br><br>Insulin detemir HS and insulin aspart before meals<br><br>vs<br><br>NPH insulin HS and insulin aspart before meals<br><br>Insulin doses were adjusted to achieve an FBG goal 4.0 to 7.0 mmol/L, PPG goal <10 mmol/L, and nocturnal goal of 4 to 7 mmol/L. | MC, OL, PG, RCT<br><br>Patients aged ≥35 years of age with type 2 diabetes for ≥12 months, $HbA_{1c}$ ≤12.0% and who had received insulin treatment for ≥2 months | N=505<br><br>26 weeks | Primary:<br>Change in $HbA_{1c}$ and FPG from baseline, nine-point self monitoring of blood glucose profile, hypoglycemia, weight gain<br><br>Secondary:<br>Not reported | Primary:<br>At 26 weeks, significant $HbA_{1c}$ reductions were observed with both the insulin detemir group (-0.2%; P=0.004) and the NPH group (-0.4%; P=0.0001). There was no significant difference in $HbA_{1c}$ reduction between the two groups (P value not reported).<br><br>At 26 weeks, both the insulin detemir group and NPH group had significant reductions in FPG from baseline (P=0.027 and P=0.026, respectively). However, differences between groups were NS (P=0.66).<br><br>There were no significant differences in mean nine-point self monitoring of blood glucose profiles between the two groups (P=0.58).<br><br>There was no significant difference in both nocturnal and total hypoglycemia between insulin detemir and NPH (P=0.95 and P=0.48, respectively).<br><br>At 26 weeks, body weight changes from baseline were significantly lower with insulin detemir compared to NPH (1.0 vs 1.8 kg, respectively; P=0.017).<br><br>Secondary:<br>Not reported |
| Fajardo Montañana et al.[88] (2008)<br><br>Insulin detemir HS | RCT, OL, PG, MC<br><br>Patients ≥18 years of age with type 2 diabetes, $HbA_{1c}$ 7.5 | N=277<br><br>26 weeks | Primary:<br>Weight changes after 26 weeks<br><br>Secondary: | Primary:<br>Mean weight gain at week 26 in the ITT population was significantly lower with insulin detemir (0.4 kg) than with NPH insulin (1.9 kg; P≤□0.0001). In the PP analysis, there were similar changes in weight (0.4 kg with insulin detemir and 2.0 kg with NPH insulin; P≤□0.0001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| and insulin aspart before meals<br><br>vs<br><br>NPH insulin HS and insulin aspart before meals<br><br>Basal insulin doses were titrated to achieve pre-breakfast PG ≤6.1 mmol/L.<br><br>Insulin aspart doses were titrated to achieve PPG ≤10.0 mmol/L.<br><br>Metformin therapy could be continued. | to 11.0%, BMI 25 to 40 kg/m$^2$, who were receiving two daily doses of insulin (at least one of them a premix) for ≥3 months; patients could also be receiving treatment with metformin; patients on other oral antidiabetic drugs were excluded. | | $HbA_{1c}$ and FPG, proportion of patients achieving $HbA_{1c}$ ≤7.0% without hypoglycemia during the last four weeks of treatment, intra-subject variability in FPG, hypoglycemia | BMI increased less with insulin detemir (0.2 kg/m$^2$) than with NPH insulin (0.8 kg/m$^2$; P≤ 0.0001).<br><br>Overall, 46.4% of insulin detemir patients showed no change or weight loss compared with 22.6% of NPH insulin patients.<br><br>Secondary:<br>At week 26, $HbA_{1c}$ decreased from 8.9 to 7.8% in the insulin detemir group and from 8.8 to 7.8% in the NPH group (P=NS).<br><br>FPG decreased from 10.8 o 8.8 mmol/L in the insulin detemir group and from 10.1 to 8.9 mmol/L in the NPH insulin group (P=NS).<br><br>The proportion of patients achieving an $HbA_{1c}$ ≤ 7.0% without hypoglycemia during the last four weeks of treatment was 27% in both treatment groups (P=NS).<br><br>Intra-subject variability of self-measured FPG at 26 weeks was lower with insulin detemir than with NPH insulin (P<0.0001).<br><br>Patients in the insulin detemir group experienced significantly less hypoglycemia than patients in the NPH insulin group. Hypoglycemia was reported by 34.7% of patients treated with insulin detemir and by 65.3% of patients receiving NPH insulin. Nocturnal hypoglycemia was reported in 30.1% of insulin detemir patients and 69.9% of NPH insulin patients (RR 0.62 for all hypoglycemic events and 0.43 for nocturnal events; P< 0.0001 for both). |
| Philis-Tsimikas et al.[89]<br>(2006)<br><br>Insulin detemir PM<br><br>vs | MC, OL, PG, RCT<br><br>Men and women ≥18 years of age, had a BMI ≤40 kg/m$^2$, type 2 diabetes for ≥12 months, insulin naïve, $HbA_{1c}$ 7.5 | N=498<br><br>20 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change in FPG, nine-point self monitoring of blood glucose | Primary:<br>Both insulin detemir groups had similar reductions in $HbA_{1c}$ compared to that of the NPH group. At 20 weeks, both evening and morning insulin detemir was found to be as effective as evening NPH (mean difference, 0.10%; 95% CI, -0.08 to 0.29 and 0.13%; 95% CI, -0.07 to 0.32, respectively). Equivalence was found between both insulin detemir groups (estimated difference, -0.03%; 95% CI, -0.21 to 0.15; P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| insulin detemir AM<br><br>vs<br><br>NPH insulin PM<br><br>Insulin doses titrated to achieve a pre-breakfast and pre-dinner FPG ≤108 mg/dL.<br><br>Existing oral antidiabetic drug therapy was continued. | to 11.0% following at least 3 months of treatment with ≥1 oral antidiabetic drug | | profile, hypoglycemia | Secondary:<br>At 20 weeks, evening insulin detemir had changes in FPG similar to those with evening NPH (mean difference, -0.46 mmol/L; 95% CI, -1.05 to 0.13). However, morning insulin detemir had significantly higher FPG than both evening NPH and evening insulin detemir (mean difference, 0.88 mmol/L; 95% CI, 0.31 to 1.5; P=0.003 and 1.33 mmol/L; 95% CI, 0.85 to 1.80; P<0.001, respectively).<br><br>Prebreakfast self monitoring of blood glucose was higher in the morning insulin detemir group in comparison to both evening groups (P<0.001). However, predinner self monitoring of blood glucose was lower in the morning insulin detemir group than that of the evening detemir and evening NPH groups (P=0.005 and P<0.001, respectively). Both evening groups resulted in similar self monitoring of blood glucose profiles.<br><br>When compared to evening NPH, evening insulin detemir resulted in a significant risk reduction in the rate of hypoglycemic episodes over 24 hours and confirmed nocturnal episodes (P=0.0019 and P=0.031, respectively). On the other hand, when comparing morning and evening detemir, the rates of hypoglycemia were statistically similar. In comparison to evening NPH, morning insulin detemir did have a significant risk reduction of 87% for confirmed nocturnal hypoglycemia (P<0.001). |
| Montanana et al.[90] (2008)<br><br>Insulin detemir SC QD<br><br>vs<br><br>NPH SC BID<br><br>All patients received insulin aspart at main meals. | PG, RCT<br><br>Type 2 diabetics ≥18 years of age with $HbA_{1c}$ 7.5 to 11.0%, BMI 25 to 40 kg/m$^2$, and receiving 2 daily doses of insulin (≥1 premix) ≥3 months | N=271<br><br>26 weeks | Primary:<br>Change in baseline body weight<br><br>Secondary:<br>Change in baseline $HbA_{1c}$ and FPG; proportion of patients achieving $HbA_{1c}$ ≤7.0% without hypoglycemia, | Primary:<br>Insulin detemir (0.4kg) resulted in significantly less weight gain compared to NPH (1.9 kg; difference, 1.5 kg; *P*<0.0001). Increases in BMI were significantly less with insulin detemir compared to NPH (difference, 0.6 kg/m$^2$; *P*<0.0001).<br><br>Secondary:<br>There was no difference in the decrease in $HbA_{1c}$ between the insulin detemir (8.9 to 7.8%) and NPH (8.8 to 7.8%) (*P* value not reported).<br><br>There was no difference in the decrease in FPG between insulin detemir (10.0 to 8.8 mmol/L) and NPH (10.1 to 8.9 mmol/L) (*P* value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Concomitant treatment with metformin was allowed. | | | incidence of hypoglycemia, safety | The proportion of patients achieving $HbA_{1c}$ ≤7.0% without hypoglycemia during the last four weeks of treatment was 27% with both treatments.<br><br>The incidence of hypoglycemia was significantly lower with insulin detemir compared to NPH (RR, 0.62 (all events) and 0.43 (nocturnal); *P*<0.0001 for both).<br><br>Both treatments were well tolerated with no major safety concerns noted and a similar incidence of adverse events with both treatments. |
| Hermansen et al.[91] (2006)<br><br>Insulin detemir BID<br><br>vs<br><br>NPH insulin BID<br><br>Basal insulin doses were adjusted to achieve pre-breakfast FBG of 108 mg/dL.<br><br>Existing oral antidiabetic drug therapy was continued. | MC, OL, PG, RCT<br><br>Adult type 2 diabetes patients with no history of insulin use, baseline $HbA_{1c}$ 8.61% for participants taking insulin detemir and 8.51% for those randomized into the NPH group | N=476<br><br>26 weeks | Primary:<br>Effect on $HbA_{1c}$<br><br>Secondary:<br>FPG, proportion of participants achieving an $HbA_{1c}$ ≤7.0%, proportion of participants achieving an $HbA_{1c}$ ≤7.0% without hypoglycemia, 10-point self monitoring of blood glucose, frequency of hypoglycemia, and weight gain | Primary:<br>After 26 weeks, $HbA_{1c}$ reductions in the insulin detemir group (-1.8%; P=0.004) did not differ significantly from reductions observed in the NPH group (-1.9%; P=NS).<br><br>Secondary:<br>After 26 weeks, the difference in mean FPG reductions between insulin detemir and NPH was not significant (0.32 mmol/L; P>0.05).<br><br>The proportion of patients achieving an $HbA_{1c}$ ≤7.0% was 70% in those taking insulin detemir and 74% with those taking NPH. The difference between treatment groups was not significant.<br><br>The proportion of patients achieving an $HbA_{1c}$ ≤7.0% without hypoglycemia was significantly higher in those taking insulin detemir (26%) compared to those taking NPH (16%; P=0.008).<br><br>There was significantly less day-to-day fluctuation of fasting self monitoring of blood glucose profiles with insulin detemir when compared to NPH (P=0.021).<br><br>There were no significant differences in mean 10-point self monitoring of blood glucose profiles between the two treatment groups (P=0.19).<br><br>There was a 47% lower risk of overall hypoglycemia with insulin detemir compared to NPH (P<0.001). There was a 55% lower risk of nocturnal hypoglycemia with insulin detemir compared to NPH |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | (P<0.001).<br><br>After 26 weeks, body weight change from baseline was significantly lower with insulin detemir (1.2 kg) compared to NPH (2.8 kg; P<0.001). |
| Strojek et al.[92] (2009)<br><br>Insulin glargine QD<br><br>vs<br><br>biphasic aspart 30 QD<br><br>Insulin doses were titrated to achieve a FPG of 5.0 to 6.1 m mol/L.<br><br>All patients also received metformin and glimepiride. | MC, NI, OL, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes who were insulin-naïve and receiving oral diabetes medications for ≥6 months, with $HbA_{1c}$ >7.0 and ≤11.0%, BMI ≤40 kg/m$^2$ | N=433<br><br>26 weeks | Primary:<br>$HbA_{1c}$ at 26 weeks<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ ≤6.5 and <7.0% without hypoglycemia after 26 weeks, $HbA_{1c}$ reduction by >1% from baseline, nine-point self-measured plasma glucose profiles, PPG increments, Diab-MedSat and safety | Primary:<br>$HbA_{1c}$ at 26 weeks was 7.1 and 7.3% with biphasic aspart and insulin glargine, respectively (difference, -0.16%, 95% CI, -0.30 to -0.02; *P*=0.029), demonstrating non-inferiority.<br><br>Secondary:<br>In both treatment groups, 25% of patients achieved $HbA_{1c}$ ≤6.5%.<br><br>In the biphasic aspart group, 44.9% of patients achieved $HbA_{1c}$ <7.0%, and 19.4% of patients achieved this value without hypoglycemia. The corresponding results with insulin glargine were 44.9 and 20.0%, respectively (*P* values not reported).<br><br>In the biphasic aspart and insulin glargine groups, 60 and 57% of patients, respectively, achieved $HbA_{1c}$ reduction by >1% (*P* value not reported).<br><br>Biphasic aspart was associated with lower post-dinner and bedtime plasma glucose compared to insulin glargine on the nine-point self-measured plasma glucose profiles (*P*<0.05). No significant differences were observed at other time points.<br><br>PPG increments were comparable between the two groups.<br><br>No significant difference was seen between biphasic aspart and insulin glargine in treatment satisfaction as measured by Diab-MedSat questionnaire (score difference, -0.11; 95% CI, -2.36 to 2.14; *P* value not reported).<br><br>Fifty-eight and 51% of patients in the biphasic aspart and insulin glargine groups, respectively, reported at least one hypoglycemic event (RR, 1.41; 95% CI, 1.03 to 1.93; *P*=0.034). The risk of nocturnal hypoglycemia was also higher with biphasic aspart compared to insulin |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | glargine (RR, 2.41; 95% CI, 1.34 to 4.34; *P*=0.003). No significant differences were seen in daytime hypoglycemia.<br><br>Treatment-emergent adverse events were reported in 51 and 48% of patients in the biphasic aspart and insulin glargine groups, respectively. Less than 1% of patients reported serious adverse events that are possibly or probably related to study medications. One treatment-emergent death was reported in the insulin glargine group and was considered not related to the study medication. No significant differences were seen in cardiovascular risk markers, waist circumference or body weight. |
| Bretzel et al.[93] (2008) APOLLO<br><br>Insulin glargine QD<br><br>vs<br><br>pre meal insulin lispro<br><br>Insulin glargine doses were titrated to achieve FPG <5.5 mmol/L.<br><br>Insulin lispro doses were titrated to achieve pre-prandial glucose <5.5 mmol/L and PPG <7.5 mmol/L. | MC, NI, OL, PG, RCT<br><br>Patients 18 to 75 years of age with type 2 diabetes for ≥1 year, $HbA_{1c}$ 7.5 to 10.5%, BMI ≤35 kg/m$^2$, FPG ≥6.7 mmol/L and receiving oral diabetes medications for ≥6 months with no dose change in the past 3 months | N=418 (intent-to-treat)<br><br>N=377 (per-protocol)<br><br>44 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline at 44 weeks<br><br>Secondary:<br>Proportion of patients with $HbA_{1c}$ ≤6.5 or ≤7.0%, change in FPG, proportion of patients with FPG ≤5.5 mmol/L, changes in nocturnal blood glucose and eight-point blood glucose profiles, percentage of patients with nocturnal, severe and symptomatic hypoglycemia | Per-protocol population was used in all efficacy endpoint analyses for non-inferiority testing. Intent-to-treat population was used subsequently for superiority testing.<br><br>Primary:<br>The adjusted mean change in $HbA_{1c}$ was -1.71 and -1.87% with insulin glargine and insulin lispro, respectively, which met the predefined 0.4% limit for non-inferiority between the two groups. Intent-to-treat analysis failed to show superiority (-1.69 vs -1.82%; *P*=0.0908).<br><br>Secondary:<br>Thirty percent and 38% of patients reached $HbA_{1c}$ ≤6.5% and 57 and 69% of patients reached $HbA_{1c}$ ≤7.0% in the insulin glargine and insulin lispro groups, respectively (*P* values not reported).<br><br>Change in FPG from baseline at 44 weeks was -4.3±2.3 and -1.8±2.3 mmol/L with insulin glargine and insulin lispro (*P*<0.0001). Significantly more patients in the glargine group achieved FPG ≤5.5 mmol/L compared to the insulin lispro group (38 vs 6%; *P* value not reported [per-protocol]; 35 vs 5%; *P*<0.001 [intent-to-treat]).<br><br>Decrease in nocturnal glucose was significantly greater with insulin glargine compared to insulin lispro (-3.3 vs -2.6 mmol/L; *P*=0.0041 [per-protocol]; -3.3 vs -2.7 mmol/L; *P*=0.0017 [intent-to-treat]).<br><br>A greater reduction was seen with insulin lispro compared to insulin |

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| The dose of oral diabetes medications remained stable throughout the entire study.<br><br>Patients who were treated with a sulfonylurea were converted to equivalent dose of glimepiride during the screening phase. | | | | glargine in PPG after breakfast, lunch, dinner and bedtime (*P*<0.05 for all).<br><br>The rate of nocturnal hypoglycemia per patient was similar between insulin glargine and insulin lispro (0.42 vs 0.27; *P*=0.0709). The rates of severe and symptomatic hypoglycemia are significantly lower with insulin glargine compared to insulin lispro (0.02 vs 0.06; *P*=0.0989; 3.46 vs 11.02; *P*<0.0001, respectively). |
| Buse et al.[94] (2009)<br>DURABLE<br><br>Insulin glargine SC QD<br><br>vs<br><br>biphasic lispro 25 SC BID | MC, OL, PG, RCT<br><br>Type 2 diabetics 30 to 80 years of age with $HbA_{1c}$ >7.0%, receiving ≥2 oral antidiabetic agents for 90 days, and BMI <45 kg/m$^2$ | N=1,045<br><br>24 weeks | Primary:<br>$HbA_{1c}$ at trial end<br><br>Secondary:<br>Change in baseline $HbA_{1c}$, body weight, and insulin dose; proportion of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%; seven-point self-monitored glucose profiles; incidence of hypoglycemia; safety | Primary:<br>Biphasic lispro 25 achieved a significantly lower final $HbA_{1c}$ compared to insulin glargine (7.3 vs 7.2%; P=0.005).<br><br>Secondary:<br>Biphasic lispro 25 had significantly greater decreases in $HbA_{1c}$ compared to insulin glargine (-1.7 vs -1.8%; P=0.005).<br><br>Biphasic lispro 25 was associated with significantly more weight gain compared to insulin glargine (2.5 vs 3.6 kg; P<0.0001).<br><br>After 24 weeks, the total daily insulin dose was significantly higher with biphasic lispro 25 compared to insulin glargine (0.40 vs 0.47 units/kg; P<0.001).<br><br>The proportion of patients achieving $HbA_{1c}$ <7.0% was significantly greater with biphasic lispro 25 compared to insulin glargine (40.3 vs 47.5%; P<0.001). There was no difference between the two treatments in the proportions of patients achieving $HbA_{1c}$ ≤6.5% (22.2 vs 24.6%; P=0.174).<br><br>Biphasic lispro 25 had a significantly higher rate of overall |

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| | | | | hypoglycemia (23.1 vs 28.0 episodes per patient-year; P=0.007), but a significantly lower rate of nocturnal hypoglycemia compared to insulin glargine (11.4 vs 8.9 episodes per patient year P=0.009). The rate of severe hypoglycemia was similar between the two treatments (0.03 vs 0.10 episodes per patient year; P=0.167).<br><br>Overall, 4.3 and 6.2% of patients receiving insulin glargine and biphasic lispro 25 experienced at least one serious adverse event (P=0.051); the rate of cardiovascular-related serious adverse events was similar between the two treatments (26 vs 29%; P=0.716). There were six and 15 adverse events leading to discontinuation with insulin glargine and biphasic lispro 25 (P=0.077). One and five deaths occurred with insulin glargine and biphasic lispro 25 (P=0.218). |
| Yki-Järvinen et al.[95] (2000)<br><br>Insulin glargine HS<br><br>vs<br><br>NPH insulin HS<br><br>Initial doses were titrated to achieve FPG target ≤120 mg/dL.<br><br>Existing oral antidiabetic drug therapy was continued. | RCT<br><br>Patients 40 to 80 years of age with type 2 diabetes for at least 3 years, BMI <40 kg/m$^2$, $HbA_{1c}$ 7.5 to 12.0%, previous oral therapy with either sulfonylureas alone or combined with acarbose, metformin, or metformin alone for at least 1 year, negative history of ketoacidosis, women of childbearing potential were required to be on contraceptive protection, willingness to | N=426<br><br>52 weeks | Primary:<br>$HbA_{1c}$<br><br>Secondary:<br>FPG, 24-hour blood glucose profile, incidence of hypoglycemia, and serum C-peptide concentrations | Primary:<br>The $HbA_{1c}$ in the insulin glargine group decreased to 8.34±0.09% at end point from baseline (P<0.001) and 8.24±0.09% in the NPH group (P<0.001).<br><br>Secondary:<br>In the group of patients that achieved target FPG ≤120 mg/dL, $HbA_{1c}$ decreased to 7.75±0.14% and 7.60±0.12% in the insulin glargine and NPH groups, respectively. However, there was no difference between groups (P values not reported).<br><br>At study end point, blood glucose concentrations were significantly lower in the insulin glargine group than the NPH group before and after dinner. However, in the group of patients that achieved target FPG, blood glucose at 3 AM was significantly lower in patients taking NPH than those taking insulin glargine (P=0.0012).<br><br>In the entire group of patients, the percentage of patients experiencing at least one symptomatic hypoglycemic episode was lower in the insulin glargine group than the NPH group. In the group of patients achieving target FPG, the percentage of patients experiencing symptomatic hypoglycemia was 33.0% and 50.7% in the insulin glargine and NPH groups, respectively (P=0.027). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | perform self monitoring of blood glucose | | | Serum C-peptide concentrations decreased similarly from baseline in both treatment groups (P<0.001). |
| Riddle et al.[96] (2003)<br><br>Insulin glargine HS<br><br>vs<br><br>NPH insulin HS<br><br>Insulin doses were titrated to achieve target FPG ≤100 mg/dL.<br><br>Existing oral antidiabetic drug therapy was continued. | CS, MC, OL, PG, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes for ≥2 years, treated with stable doses of 1 or 2 oral antidiabetic drug for ≥3 months, BMI 26 to 40 kg/m$^2$, $HbA_{1c}$ 7.5 to 10.0%, FPG ≥140 mg/dL at screening | N=764<br><br>24 weeks | Primary:<br>Percentage of patients achieving an $HbA_{1c}$ ≤7.0% without a single instance of symptomatic nocturnal hypoglycemia confirmed by plasma-referenced glucose ≤72 mg/dL<br><br>Secondary:<br>Changes from baseline in $HbA_{1c}$, FPG, and weight; percentage of patients achieving an $HbA_{1c}$ ≤7.0% or FPG ≤100 mg/dL independent of the occurrence of hypoglycemia; percentage of patients achieving FPG ≤100 mg/dL without confirmed hypoglycemia; overall rates of | Primary:<br>The percentage of patients reaching a target $HbA_{1c}$ ≤7.0% without a single instance of symptomatic nocturnal hypoglycemia was achieved by more patients taking insulin glargine than patients taking NPH (32.2 vs 26.7%, respectively; P<0.05).<br><br>Secondary:<br>Mean $HbA_{1c}$ at end point was 6.96% with insulin glargine and 6.97% with NPH (between-treatment difference, -0.03%; 95% CI, -0.13 to 0.08; P=NS). Both groups also achieved comparable decreases in FPG at end point (between-treatment difference, -3.6 mg/dL; 95% CI, -8.82 to 1.62; P=NS). Weight increased similarly from baseline to end point in both groups (between-treatment difference, 0.2 kg; 95% CI, -0.24 to 0.68; P=NS).<br><br>The $HbA_{1c}$ ≤7.0% target was reached by 58.0% of patients on insulin glargine and 57.3% of patients in the NPH group.<br><br>The goal FPG ≤100 mg/dL was achieved by 36.2% of patients on insulin glargine and 34.4% of patients on NPH. This target was achieved without hypoglycemia more often by patients taking insulin glargine. FPG ≤100 mg/dL without documented nocturnal hypoglycemia was achieved by 22.1% of patients taking insulin glargine compared to 15.9% of patients taking NPH (P<0.03).<br><br>The rates of hypoglycemia (events/patient-year) with insulin glargine vs NPH were 13.9 vs 17.7, respectively for all symptomatic events (P<0.02) and 9.2 vs 12.9, respectively, for all confirmed events (P<0.005). |

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| | | | symptomatic hypoglycemia | |
| Rosenstock et al.[97] (2009)<br><br>Insulin glargine HS<br><br>vs<br><br>NPH insulin BID<br><br>Insulin doses were titrated to achieve FPG ≤120 mg/dL during the first 3 years of the study, then FPG ≤100 mg/dL during the last 2 years of the study.<br><br>Oral antidiabetic drug and/or prandial insulin could be continued or modified during the trial, and regular insulin could be added with meals at the investigator's discretion. | MC, OL, PG, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes with $HbA_{1c}$ 6.0 to 12.0% who were treated with oral antidiabetic drugs or insulin (alone or in combination) for ≥1 year | N=1,017<br><br>5 years | Primary:<br>Percentage of patients with three or more step progression in Early Treatment Diabetic Retinopathy Study score after five years of treatment with either insulin glargine or NPH insulin<br><br>Secondary:<br>$HbA_{1c}$, FPG, and hypoglycemia | Primary:<br>In the ITT analysis, 12.5% of patients in the insulin glargine group experienced a ≥3 step progression in Early Treatment Diabetic Retinopathy Study score after five years compared to 14.6% of patients receiving NPH insulin (difference, −2.10%; 95% CI, −6.29 to 2.09). In the PP analysis, 14.2 and 15.7% of patients experienced a ≥3 step progression in Early Treatment Diabetic Retinopathy Study score after five years, respectively (difference, -1.98%; 95% CI, -7.02 to 3.06).<br><br>Secondary:<br>After five years, the mean FPG in the insulin glargine group was 7.8 and 7.7 mmol/L in the NPH insulin group (ITT population).<br><br>The proportion of patients achieving FPG ≤5.6 mmol/L was 28.5% with insulin glargine and 24.3% with NPH insulin.<br><br>After five years, the mean $HbA_{1c}$ (last observation carried forward) improved from a baseline of 8.4 and 8.3 to 7.8 and 7.6% for patients in the insulin glargine and NPH insulin groups, respectively (difference, 0.21%; P=0.0053).<br><br>Weight gain was 3.7 kg with insulin glargine compared to 4.8 kg with NPH insulin (ITT; P=0.0505).<br><br>The use of NPH insulin was associated with a greater incidence of severe hypoglycemia than insulin glargine (11.1 vs 7.6%, respectively; P=0.0439). However, there was no significant difference in symptomatic hypoglycemia (P=0.1366) or nocturnal hypoglycemia (P=0.2248) between the treatment groups. |
| Fritsche et al.[98] (2003)<br><br>Insulin glargine AM and glimepiride 3 mg | MC, OL, PG, RCT<br><br>Patients with type 2 diabetes <75 years of age, previously on oral therapy with | N=700<br><br>28 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to end point, frequency of patients who | Primary:<br>Over the 24-week treatment period, $HbA_{1c}$ levels improved by -1.24% (two-sided 90% CI, -1.10 to -1.38) with morning insulin glargine, -0.96% (90% CI, -0.81 to -1.10) with bedtime insulin glargine and -0.84% (90% CI, -0.69 to -0.98) with bedtime NPH (P values not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| QD<br><br>vs<br><br>insulin glargine HS and glimepiride 3 mg QD<br><br>vs<br><br>NPH insulin HS and glimepiride 3 mg QD | any sulfonylurea as monotherapy or in combination with metformin or acarbose, BMI <35 kg/m$^2$, FPG ≥120 mg/dL, $HbA_{1c}$ 7.5 to 10.5% | | experienced hypoglycemic episodes during the study<br><br>Secondary:<br>$HbA_{1c}$ ≤7.5%, FBG ≤100 mg/dL, response rates, mean 24-hour blood glucose values, hypoglycemic events and adverse events | Improvement in $HbA_{1c}$ was significant in patients receiving morning insulin glargine than in patients receiving NPH (-0.40%; 90% CI, -0.23 to -0.58; P<0.001) and bedtime insulin glargine (-0.28%; 90% CI, -0.11 to -0.46; P=0.008).<br><br>Secondary:<br>More patients in the morning insulin glargine group achieved $HbA_{1c}$ level of <7.5% (43%) than patients in the bedtime NPH (32%) and bedtime insulin glargine groups (33%; P=0.021).<br><br>FPG levels improved in all three groups. The average reduction in FPG level achieved over the 24-week treatment did not differ among the groups (P>0.2).<br><br>The morning insulin glargine group showed a greater decrease in mean daily blood glucose levels compared to both the bedtime NPH group (P<0.001) and the bedtime insulin glargine group (P=0.002).<br><br>Hypoglycemic events were similar among the three groups. The number of patients experiencing nocturnal hypoglycemia was lower in both the morning and bedtime insulin glargine groups than with the bedtime NPH group (P<0.001). Fewer patients experienced symptomatic hypoglycemia with bedtime insulin glargine (43%) than with bedtime NPH (58%; P=0.001) and morning insulin glargine (56%; P=0.004).<br><br>Adverse event rates were similar in all three groups (P values not reported). |
| Pan et al.[99] (2007)<br><br>Insulin glargine HS and glimepiride 3 mg QD<br><br>vs | MN, NI, OL, PG, RCT<br><br>Insulin-naïve Asian patients 40 to 80 years of age with type 2 diabetes and random venous plasma glucose | N=448<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to endpoint<br><br>Secondary:<br>Mean FPG level, eight-point blood glucose profiles, proportion of | Primary:<br>The insulin glargine group had a decrease of -1.10% in $HbA_{1c}$ vs -0.92% in the NPH group. There was not a statistically significant difference between both groups (P=0.0631). The results were confirmed in a full analysis set, the difference between adjusted mean changes in the two groups was 0.22 (95% CI, 0.02 to 0.42; P=0.0319).<br><br>Secondary:<br>FPG decreased to a similar extent in both the insulin glargine and NPH groups (-106 and -104 mg/dL, respectively; P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| NPH insulin HS and glimepiride 3 mg QD | concentration ≥11.1 mmol/L, FPG ≥7 mmol/L, or PPG ≥11.1 mmol/L 2 hours after oral glucose tolerance test, poorly controlled on oral antidiabetic drug for ≥3 months prior to study entry, BMI 20 to 35 kg/m$^2$, $HbA_{1c}$ 7.5 to 10.5%, and FPG >120 mg/dL | | patients with $HbA_{1c}$ <7.5%, proportion of combined responders (defined as $HbA_{1c}$ <7.5% and FPG ≤120 mg/dL), change in BMI, hypoglycemia | At study end, the eight-point blood glucose profiles were similar in both the insulin glargine and NPH groups, except at postdinner time, when the use of insulin glargine resulted in lower glucose concentrations (P=0.0436). The insulin glargine group had greater decreases in daily blood glucose levels than the NPH group (-94 vs -80 mg/dL, respectively; P=0.018).<br><br>The proportion of patients achieving $HbA_{1c}$ <7.5% at the end of the study was greater for the insulin glargine group than the NPH group (38.1 vs 30.3%, respectively). This was also consistent with the proportion of patients achieving target FPG (62.3 vs 58.7%, respectively). In the insulin glargine group, a greater proportion of patients achieved $HbA_{1c}$ <7.5% without experiencing nocturnal symptomatic hypoglycemia (P=0.0174).<br><br>Both groups had similar changes in BMI from baseline (1.40 and 1.29 kg/m$^2$ in the insulin glargine and NPH groups, respectively).<br><br>The number of hypoglycemic episodes was significantly lower with insulin glargine than with NPH (P<0.004). These differences were seen in particular with symptomatic hypoglycemia (P<0.0003), severe hypoglycemia (P<0.03), and nocturnal hypoglycemia (P<0.001). |
| Eliaschewitz et al.[100] (2006)<br><br>Insulin glargine HS and glimepiride 4 mg QD<br><br>vs<br><br>NPH insulin HS and glimepiride 4 mg QD | MC, OL, RCT<br><br>Men and women ≤75 years of age with type 2 diabetes, who had not achieved good metabolic control on oral antidiabetic drugs for at least 6 months, with $HbA_{1c}$ levels 7.5 to 10.5%, FPG ≥100 mg/dL, and BMI | N=528<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to end of study<br><br>Secondary:<br>Percentage of patients who responded to treatment (defined as those who achieved $HbA_{1c}$ ≤7.5% and FPG ≤100 mg/dL | Primary:<br>At 24 weeks, both groups demonstrated equivalence in change in $HbA_{1c}$ (adjusted mean difference, -0.047; 90% CI, -0.232 to 0.138). Based on equivalence result, an analysis was conducted and also revealed no significant difference between groups (adjusted mean difference, -0.029; 90% CI, -0.210 to 0.153; P=0.795).<br><br>Secondary:<br>The percentages of responders were similar in both the insulin glargine group and NPH group for $HbA_{1c}$ ≤7.5% (50.4 vs 48.0%, respectively; P=0.529) and FPG ≤100 mg/dL (42.1 vs 39.8%, respectively; P=0.752).<br><br>There was no significant difference between groups in changes in FPG (P=0.298). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Insulin doses were titrated to achieve target FPG ≤100 mg/dL. | ≤35 kg/m$^2$ | | by end of study), change in FPG from baseline, hypoglycemia | The insulin glargine group had a lower RR of hypoglycemia than the NPH group (RR, 1.27; 95% CI, 1.03 to 1.57). There was also a greater reduction in the risk of nocturnal hypoglycemia (RR, 1.2; 95% CI, 1.09 to 1.37) and confirmed nocturnal events (RR, 1.19; 95% CI, 1.07 to 1.31) in the insulin glargine group than the NPH group (P value not reported). |
| Yki-Järvinen et al.[101] (2006)<br><br>Insulin glargine HS and metformin (G+MET)<br><br>vs<br><br>NPH insulin HS and metformin (NPH+MET)<br><br>Insulin doses were titrated to achieve an FPG 72 to 100 mg/dL in both groups. | MC, OL, PG, RCT<br><br>Men and women 35 to 75 years of age with type 2 diabetes previously treated with a stable dose of sulfonylurea and metformin (>1.5 g) or metformin alone for at least 3 months prior to screening, with a BMI 20 to 40 kg/m$^2$, $HbA_{1c}$ ≥8.0%, FPG ≥7 mmol/L measured during self monitoring of blood glucose between 4 and 2 weeks prior to study start, and fasting C-peptide ≥0.33 nmol/L | N=110<br><br>36 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Diurnal glucose concentrations, symptomatic hypoglycemia | Primary:<br>At 36 weeks, $HbA_{1c}$ decreased from 9.13±0.15% to 7.14±0.12% and from 9.26±0.15% to 7.16±0.14% in the G+MET and NPH+MET groups, respectively. The changes in $HbA_{1c}$ were determined to be not significant between groups (P value not reported).<br><br>Secondary:<br>The diurnal profiles were consistently lower in the G+MET group compared to the NPH+MET group (8.6±0.3 vs 10.1±0.3 mmol/L, respectively; P=0.002).<br><br>During the first 12 weeks, the G+MET group had significantly lower number of episodes of symptomatic hypoglycemia than the NPH+MET group, but the rates became similar thereafter. The frequency of hypoglycemia averaged 5.4 and 8.0 episodes/patient-year for the G+MET and NPH+MET groups, respectively (P=0.12). |
| Holman et al.[102] (2007) | MC, OL, RCT<br><br>Patients ≥18 years of | N=708<br><br>1 year | Primary:<br>$HbA_{1c}$ at one year | Primary:<br>At 52 weeks, the reduction in $HbA_{1c}$ from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 0.8% in the basal group. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Biphasic insulin aspart 30 BID<br><br>vs<br><br>insulin aspart TID before meals<br><br>vs<br><br>insulin detemir HS to BID (AM and HS)<br><br>Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG 90 to 126 mg/dL.<br><br>Existing oral antidiabetic drug regimens were continued. | age with type 2 diabetes who had not been previously treated with insulin, $HbA_{1c}$ 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for ≥4 months, and BMI ≤40 kg/m$^2$ | | Secondary:<br>Proportion of patients with $HbA_{1c}$ ≤6.5%, proportion of patients with ≤ 6.5% but without hypoglycemia during weeks 48 to 52, rate of hypoglycemia, weight gain, eight-point self monitoring blood glucose | The difference between the $HbA_{1c}$ levels in the biphasic group (7.3%) and the prandial group (7.2%) were not significant (P=0.08); however, the $HbA_{1c}$ level was higher in the basal group (7.6%; P<0.001 for both comparisons with the basal group).<br><br>Secondary:<br>The proportion of patients with an $HbA_{1c}$ ≤6.5% was 17% in the biphasic group and 23.9% in the prandial group (P=0.08). The proportion of patients in the basal group was 8.1%, which was lower than the other groups (P=0.001 for the comparison with the biphasic group and P<0.001 for the comparison with the prandial group).<br><br>The proportion of patients with an $HbA_{1c}$ ≤6.5% without hypoglycemia during weeks 48 to 52 were 52.5, 43.9, and 78.9% in the biphasic, prandial, and basal groups, respectively (P=0.001).<br><br>The proportion of patients with an $HbA_{1c}$ level of ≤7.0% was significantly different between the basal group (27.8%) and each of the two other groups (biphasic group, 41.7%; prandial group, 48.7%; P<0.001 for both comparisons).<br><br>Patients gained weight on all regimens, with a greater increase in the prandial group (5.7 kg; P<0.001 vs basal) than in the biphasic group (4.7 kg; P=0.005 vs prandial and P<0.001 vs basal) or the basal group (1.9 kg).<br><br>There were no significant differences in overall mean self monitoring blood glucose among the treatment groups.<br><br>Overall rates of hypoglycemia were 91.9% in the biphasic group (P=0.08 vs prandial), 96.2% in the prandial group (P<0.001 vs basal), and 73.9% in the basal group (P<0.001 vs biphasic). The mean numbers of hypoglycemic events per patient per year were 5.7 in the biphasic group, 12.0 in the prandial group, and 2.3 in the basal group. |
| Holman et al.[103] (2009)<br><br>Biphasic insulin | MC, OL, RCT<br><br>Patients ≥18 years of age with type 2 | N=708<br><br>3 years | Primary:<br>$HbA_{1c}$ at three years | Primary:<br>The mean reduction in $HbA_{1c}$ from baseline to year three was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| aspart 30 BID<br><br>vs<br><br>insulin aspart TID before meals<br><br>vs<br><br>insulin detemir HS to BID (AM and HS)<br><br>Insulin doses were titrated to achieve pre-meal capillary blood glucose 72 to 99 mg/dL or PPG 90 to 126 mg/dL.<br><br>Existing oral antidiabetic drug regimens were continued. | diabetes who had not been previously treated with insulin, $HbA_{1c}$ 7.0 to 10.0%, on maximum tolerated doses of metformin and a sulfonylurea for ≥4 months, and BMI ≤40 kg/$m^2$ | | Secondary:<br>Proportion of patients with $HbA_{1c}$ ≤6.5%, rate of hypoglycemia, weight gain, self monitoring blood glucose | Secondary:<br>The proportion of patients with an $HbA_{1c}$ ≤6.5% was 31.9% in the biphasic group and 44.7%% in the prandial group (P=0.006). The proportion of patients in the basal group was 43.2% (P=0.03 vs biphasic).<br><br>The proportion of patients with an $HbA_{1c}$ ≤7.0%was 49.4% in the biphasic group, 67.4% in the prandial group (P<0.001 vs biphasic) and 63.2% in the basal group (P=0.02 vs biphasic).<br><br>Self monitoring blood glucose values were significantly lower in the prandial group than in the biphasic group (P=0.001), but were not significantly different than in the basal group (P=0.06). No significant differences were seen in fasting glucose values in the three groups. A greater mean reduction in postprandial glucose values was seen in the prandial group than in either the biphasic group (P<0.001) or the basal group (P=0.007), with a greater reduction in the basal group than in the biphasic group (P=0.04). The reduction in 3 a.m. glucose values was significantly greater in the basal group than in the prandial group (P=0.02)<br><br>Patients gained weight on all regimens, with a greater increase in the prandial group (6.4 kg; P<0.001 vs basal) than in the biphasic group (5.7 kg; P=0.20 vs prandial and P=0.005 vs basal) or the basal group (3.6 kg).<br><br>Overall rates of hypoglycemia were 49.4% in the biphasic group (P=0.68 vs prandial), 51.0% in the prandial group (P=0.14 vs basal), and 44.0% in the basal group (P=0.29 vs biphasic). The median number of hypoglycemic events per patient per year during the trial was 3.0 in the biphasic group, 5.5 in the prandial group, and 1.7 in the basal group.<br><br>At 3 years, no differences were seen in changes from baseline in either systolic or diastolic blood pressure, high-density lipoprotein or low-density lipoprotein cholesterol, triglycerides, or the ratio of urinary albumin to creatinine, although the differences in high-density lipoprotein cholesterol were significant (P=0.03). |
| Garber et al.[104] (2007) | MC, OL, PG, pooled analysis, RCT | N=1,374<br><br>22 to 26 | Primary:<br>Difference in $HbA_{1c}$ at study | Primary:<br>$HbA_{1c}$ with insulin detemir was as effective as NPH after 22 to 26 weeks (mean treatment difference, 0.035%; 95% CI, -0.114 to 0.183 for older |

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| Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment<br><br>vs<br><br>NPH insulin QD or BID and prandial insulin (insulin aspart or regular insulin) or oral antidiabetic drug treatment<br><br>Insulin doses were adjusted to achieve target FBG 72 to 126 mg/dL, FPG <108 mg/dL, PPG <180 mg/dL or <162 mg/dL. | Patients ≥18 years of age with type 2 diabetes for at least 1 year treated with insulin, insulin analogs, or oral antidiabetic drugs for at least 2 months, $HbA_{1c}$ ≤12.0% (in study 3, patients with $HbA_{1c}$ 7.5 to 10% were enrolled); patients were stratified to older (aged ≥65 years) and younger (18 to 64 years of age) subgroups | weeks | endpoint between younger and older patients<br><br>Secondary:<br>Glucose variability, FPG, insulin doses, body weight, hypoglycemia | persons and 0.100%; 95% CI, -0.017 to 0.217 for younger persons; P value not reported).<br><br>Secondary:<br>After 22 to 26 weeks, within-person variation was significantly lower with insulin detemir than with NPH for older persons (24.3 vs 27.2 mg/dL for insulin detemir and NPH, respectively; P<0.05) and for younger persons (22.6 vs 25.8 mg/dL for insulin detemir and NPH, respectively; P<0.001).<br><br>FPG with insulin detemir was similar to that with NPH after 24 or 26 weeks for both older and younger patients (mean treatment difference, 0.97 mg/dL; 95% CI, -8.01 to 9.95 for older persons and 4.69 mg/dL; 95% CI, -2.30 to 11.67 for younger persons; P value not reported).<br><br>The mean daily insulin dose was 0.63±0.45 IU/kg for insulin detemir and 0.48±0.28 IU/kg for NPH in younger patients. Older patients had similar doses to younger patients (0.59±0.44 IU/kg for insulin detemir and 0.46±0.26 IU/kg for NPH; P value not reported).<br><br>The RR for overall hypoglycemia was statistically lower with insulin detemir than with NPH in both older and younger patients (0.59; P=0.002 and 0.75; P=0.022, respectively). The RR for all nocturnal episodes was significantly lower with insulin detemir (P<0.001) in younger patients, but was not significant in older patients. |
| Raslová et al.[105] (2007)<br><br>Insulin detemir QD or BID and prandial insulin (insulin aspart or regular insulin)<br><br>vs | PG, pooled analysis, RCT<br><br>Patients with insulin-treated type 2 diabetes | N=900<br><br>22 to 24 weeks | Primary:<br>Weight gain, $HbA_{1c}$<br><br>Secondary:<br>Not reported | Primary:<br>Patients taking insulin detemir had little weight gain, regardless of BMI at study entry. However, patients taking NPH had increased weight gain as baseline BMI increased (P=0.025).<br><br>Glycemic control was similar with both treatment groups (P value not reported).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| NPH insulin QD or BID and prandial insulin (insulin aspart or regular insulin) | | | | |
| Siegmund et al.[106] (2007)<br><br>Insulin glargine plus premeal rapid-acting insulin analogs<br><br>vs<br><br>NPH plus premeal rapid-acting insulin analogs | OS, PRO<br><br>Patients with type 2 diabetes | N=119<br><br>18 months | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Weight gain, incidence of hypoglycemia | Primary:<br>For the insulin glargine group, results showed statistically significant reductions in $HbA_{1c}$ compared to baseline (-0.49%; 95% CI, -0.26 to -0.71; P<0.001). However, the reduction from baseline in $HbA_{1c}$ for the NPH group was determined to be not significant (-0.12%; 95% CI, -0.31 to 0.06; P=0.189). After 18 months, the difference between the two treatment groups was 0.37% (P<0.015).<br><br>Secondary:<br>Average weight gain was significantly higher in the NPH group than in the glargine group (2.10 vs 0.25 kg, respectively; P=0.025).<br><br>Although there was a lower risk of hypoglycemia in the insulin glargine group than in the NPH group (0.50 vs 0.71 episodes/patient/month, respectively), the results did not reach statistical significance (P=0.081). |
| Rosenstock et al.[107] (2005)<br><br>Insulin glargine HS<br><br>vs<br><br>NPH insulin QD or BID | MA<br><br>MA of 4 randomized trials in type 2 diabetics comparing insulin glargine to NPH, baseline $HbA_{1c}$ 8.8% in the insulin glargine group and 8.7% in the NPH group | N=2,304<br><br>20 to 24 weeks | Primary:<br>Incidence of hypoglycemia<br><br>Secondary:<br>Effect on $HbA_{1c}$, percentage of patients reaching target $HbA_{1c}$ ($\leq$7.0%), effect on FPG, and insulin dose | Primary:<br>Significant reductions in symptomatic hypoglycemic risk (-11%; P=0.0006) and nocturnal hypoglycemic risk (-26%; P<0.0001) were reported with insulin glargine compared to NPH.<br><br>Secondary:<br>No significant difference was noted between groups in $HbA_{1c}$ reduction or percentage of patients reaching target $HbA_{1c}$ $\leq$7.0%.<br><br>FPG was significantly lower with insulin glargine (155 mg/dL) compared to NPH (161 mg/dL; P=0.0233).<br><br>Both groups had similar mean basal and total insulin doses at all study endpoints. |
| Horvath et al.[108] (2007) | MA<br><br>Analysis of 8 | N=2,293<br><br>24 to 52 | Primary:<br>Change in $HbA_{1c}$ from baseline to | Primary:<br>In a MA of studies with relevant data available comparing insulin glargine vs NPH when both agents were administered in the evening, the |

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| Insulin analogs (insulin glargine or insulin detemir)<br><br>vs<br><br>NPH insulin | studies comparing long-acting insulin analogs to NPH in patients with type 2 diabetes | weeks | endpoint<br><br>Secondary: Number of overall, severe, and nocturnal hypoglycemia | WMD of change of $HbA_{1c}$ from baseline was estimated to be 0.1% (95% CI, -0.1 to 0.2; P=0.49) in favor of NPH. In all studies comparing evening insulin glargine to NPH, the WMD of change of $HbA_{1c}$ was estimated to be 0.00% (95% CI, -0.1 to 0.1; P=0.93) which confirmed the previous result.<br><br>In both analyses that compared change in $HbA_{1c}$ with insulin detemir to NPH, NPH was favored (WMD, 0.1%; 95% CI, 0.01 to 0.20; P=0.03 when standard deviations were calculated and 0.2%; 95% CI, 0.02 to 0.30; P=0.08 using pooled standard deviations). Even though this result indicated a statistically significant difference in change of $HbA_{1c}$ between insulin detemir and NPH, the difference was within the "non-inferiority" margin of 0.4% for both studies.<br><br>Secondary:<br>In both comparisons of insulin glargine vs NPH and insulin detemir vs NPH, both long-acting agents had statistically lower rates of severe hypoglycemia (OR, 0.70; 95% CI, 0.40 to 1.23; P value not reported and 0.50; 95% CI, 0.18 to 1.38; P=0.18, respectively).<br><br>Insulin glargine was found to have a lower frequency of symptomatic hypoglycemia than NPH (RR, 0.84; 95% CI, 0.75 to 0.95; P=0.005). In terms of overall hypoglycemia, there was no difference in the rates of at least one hypoglycemic episode between insulin glargine in the morning, insulin glargine in the evening, and NPH at bedtime (74, 68 and 75%, respectively; P=NS).<br><br>When comparing insulin detemir to NPH, insulin detemir had significantly lower rates of symptomatic and overall hypoglycemia (RR, 0.56; 95% CI, 0.42 to 0.74; P<0.001 and 0.82; 95% CI, 0.74 to 0.90; P<0.0001, respectively).<br><br>Both insulin glargine and insulin detemir resulted in significantly lower rates of nocturnal hypoglycemia in comparison to NPH (RR, 0.66; 95% CI, 0.55 to 0.80; P<0.0001 and 0.63; 95% CI, 0.52 to 0.76; P<0.00001, respectively). |
| Bazzano et al.[109] | MA, SR (12 | N=4,385 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (2008)<br><br>Insulin glargine<br><br>vs<br><br>NPH insulin | RCTs)<br><br>Patients with type 2 diabetes with or without oral antidiabetic agents, and not receiving insulin | ≥4 weeks | Change in baseline $HbA_{1c}$, FPG, and body weight<br><br>Secondary:<br>Incidence of hypoglycemia | Changes in $HbA_{1c}$, FPG, and body weight demonstrate positive values favoring insulin glargine and negative values favoring NPH. The pooled net change for FPG was 0.21 mmol/L (95% CI, -0.02 to 0.45). Final $HbA_{1c}$ was 7.9 and 7.7% with insulin glargine and insulin NPH, respectively. Pooled net change in body weight was -0.33 kg (95% CI, -0.61 to -0.06).<br><br>Secondary:<br>The proportions of patients reporting any (59.0 vs 53.0%; P<0.001), symptomatic (51.4 vs 42.9%; P<0.001) and nocturnal hypoglycemia (33.3 vs 19.1%; P<0.001) were significantly greater with insulin NPH. The rates of confirmed (10.0 vs 6.3%; P=0.11) and severe hypoglycemia (2.5 vs 1.4%; P=0.07) were not different between the two treatments. |
| Davidson et al.[110] (2009)<br><br>Biphasic insulin aspart 30 (BIAsp 30)<br><br>vs<br><br>biphasic human insulin 30 (BHI 30) | MA<br><br>Patients with type 2 diabetes who received treatment with biphasic insulin aspart 30 or biphasic human insulin 30 | N=1,674 (9 trials)<br><br>12 to 48 weeks | Primary:<br>Overall rate of nocturnal hypoglycemia (all major, minor, and symptoms-only)<br><br>Secondary:<br>Major hypoglycemia, minor hypoglycemia, daytime hypoglycemia, overall hypoglycemia (the sum of all major, minor, and symptoms-only episodes), change in weight from baseline to 12 to 16 weeks of treatment | Primary:<br>No significant difference was found between treatments with respect to the rate of overall hypoglycemia (RR, 1.08; 95% CI, 0.94 to 1.24; P=NS).<br><br>Secondary:<br>BIAsp 30 had a significantly lower rate of nocturnal hypoglycemia than BHI 30 (RR, 0.50; 95% CI, 0.38 to 0.67; P<0.01).<br><br>BHI 30 was associated with a significantly lower rate of daytime hypoglycemia (RR, 1.24; 95% CI, 1.08 to 1.43; P<0.01).<br><br>Significantly fewer patients experienced a major hypoglycemic episode with BIAsp 30 compared with BHI 30 (P<0.05).<br><br>Rates of minor hypoglycemia were not significantly different between treatments.<br><br>BIAsp 30 treatment was associated with a larger reduction in PPG than BHI 30 (P<0.01).<br><br>BHI 30 treatment was associated with a significantly larger reduction in FPG than BIAsp 30 (P<0.01).<br><br>There were no significant differences in $HbA_{1c}$ among the treatment |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | groups.<br><br>Both BIAsp 30 and BHI 30 were associated with an increase in weight from base line (0.2 and 0.7 kg, respectively; P=NS). |
| Fakhoury et al.[111] (2008)<br><br>NPH QD<br><br>vs<br><br>insulin detemir in the evening<br><br>vs<br><br>insulin glargine in the evening<br><br>All patients remained on oral diabetes medications. | MA (5 OL, PG, RCTs)<br><br>Patients between 55.5 and 61.0 years of age with type 2 diabetes who were insulin-naïve and currently receiving oral diabetes medications, with $HbA_{1c}$ 8.6 to 9.6% and BMI of 28.5 to 32.0 kg/m$^2$ | N=2,092<br><br>5 to 12 months | Primary:<br>Weight gain, hypoglycemia, $HbA_{1c}$<br><br>Secondary:<br>Not reported | Primary:<br>Patients receiving insulin detemir experienced significantly less weight gain compared to those receiving insulin glargine (WMD, -1.22 kg; 95% CI, -2.15 to -0.29; P=0.01).<br><br>Fewer episodes of hypoglycemia was reported with insulin detemir compared to insulin glargine (OR, 0.52; 95% CI, 0.28 to 0.98; P=0.044).<br><br>No significant difference was seen in the mean $HbA_{1c}$ between insulin detemir and insulin glargine (standardized mean difference, 0.09; 95% CI, -0.16 to 0.33; P=0.48).<br><br>No significant differences were seen in weight gain, incidence of hypoglycemia and mean $HbA_{1c}$ between NPH and insulin glargine.<br><br>Secondary:<br>Not reported |
| Singh et al.[112] (2009)<br><br>Insulin analogs<br><br>vs<br><br>conventional insulin | MA<br><br>Adult and pediatric patients with type 1 diabetes and type 2 diabetes, and women with gestational diabetes | 117 Trials<br><br>4 to 30 weeks | Primary:<br>$HbA_{1c}$ and hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>*Adults – Type 1 Diabetes Mellitus*<br>The use of insulin lispro resulted in a lower $HbA_{1c}$ (difference, –0.09%, 95% CI, –0.16 to –0.02), a lower risk of severe hypoglycemia (RR, 0.80; 95% CI, 0.67 to 0.96) and a lower rate of nocturnal hypoglycemia (RR, 0.51; 95% CI, 0.42 to 0.62) compared to regular insulin. For overall hypoglycemia, the rate was similar between the groups receiving insulin lispro and those receiving regular human insulin.<br><br>For insulin aspart, the mean $HbA_{1c}$ was lower than with regular insulin (difference, –0.13%; 95% CI, –0.20 to –0.07). There were no significant differences between treatments in the risk of severe hypoglycemia or the rate of overall hypoglycemia. The rate of nocturnal hypoglycemia (reported in one study) in patients receiving insulin aspart (CSII) was |

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| | | | | significantly lower than in patients receiving regular insulin (RR, 0.55; 95% CI, 0.43 to 0.70).<br><br>There was no significant difference in $HbA_{1c}$ (reported in one study) with insulin lispro or insulin aspart administered through CSII (difference, 0.25%; 95% CI, –0.20 to 0.71). There was also no significant difference in the rates of nocturnal hypoglycemia among the two treatment groups (RR, 1.20; 95% CI, 0.89 to 1.68). The rate of overall hypoglycemia was higher with insulin lispro than with insulin aspart (RR, 1.49; 95% CI, 1.37 to 1.63).<br><br>Insulin glargine led to greater reductions in $HbA_{1c}$ compared to NPH insulin (difference, –0.11%; 95% CI, –0.21 to –0.02). There were no significant differences for any type of hypoglycemia when the same bolus insulin was used in each treatment arm.<br><br>There was no significant difference in $HbA_{1c}$ with insulin detemir and NPH insulin (difference, –0.06%; 95% CI, –0.13 to 0.02). There was a lower risk of severe hypoglycemia (RR, 0.74; 95% CI, 0.58 to 0.96) and nocturnal hypoglycemia (RR, 0.92; 95% CI, 0.85 to 0.98) with insulin detemir compared to NPH; however, there was no difference in overall hypoglycemia.<br><br>There was no significant difference in $HbA_{1c}$ (reported in one study) between insulin detemir and insulin glargine (difference, –0.03%; 95% CI, –0.26 to 0.20). The risk of severe hypoglycemia (RR, 0.25; 95% CI, 0.07 to 0.86), as well as the risk for severe and nocturnal hypoglycemia were significantly lower with insulin detemir.<br><br>*Children and Adolescents – Type 1 Diabetes Mellitus*<br>Only one trial compared insulin lispro with regular insulin in adolescents with type 1 diabetes. This study found no difference in $HbA_{1c}$ (difference, –0.01%; 95% CI, –0.21 to 0.19) or the risk of severe hypoglycemia (RR, 1.00; 95% CI, 0.29 to 3.43) among the two treatment groups. The risk of nocturnal hypoglycemia (RR, 0.61; 95% CI, 0.57 to 0.64) and overall hypoglycemia favored insulin lispro. |

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| | | | | There was no significant difference between insulin lispro and regular insulin in preadolescent patients for the following outcomes: $HbA_{1c}$ (difference, 0.14%; 95% CI, –0.18 to 0.46), risk of severe hypoglycemia (RR, 0.69; 95% CI, 0.24 to 2.01), rates of nocturnal hypoglycemia (RR, 0.96; 95% CI, 0.74 to 1.26), and overall hypoglycemia.<br><br>Only one trial compared insulin aspart and regular insulin in preadolescent patients with type 1 diabetes. This study found no difference in $HbA_{1c}$ or risk of overall hypoglycemia among the treatment groups.<br><br>There was no significant difference between insulin glargine and intermediate-acting insulins (mostly NPH insulin) in children and adolescents with type 1 diabetes in $HbA_{1c}$ (difference, –0.25%; 95% CI, –0.55 to 0.05) or any type of hypoglycemia.<br><br>Only one trial compared insulin detemir with NPH insulin in children and adolescents with type 1 diabetes. This study showed no significant differences between treatments in $HbA_{1c}$ (difference, 0.10%; 95% CI, –0.10 to 0.30) or severe hypoglycemia (RR, 0.80; 95% CI, 0.50 to 1.28). The risk of nocturnal hypoglycemia (RR, 0.85; 95% CI, 0.77 to 0.94), as well as for nocturnal and overall hypoglycemia demonstrated small, statistically significant benefits in favor of insulin detemir.<br><br>*Adults – Type 2 Diabetes Mellitus*<br>There was no significant difference in $HbA_{1c}$ (difference, –0.03%; 95% CI, –0.12 to 0.06) or risk of severe hypoglycemia (RR, 0.43; 95% CI, 0.08 to 2.37), nocturnal hypoglycemia (RR, 1.63; 95% CI, 0.71 to 3.73) or overall hypoglycemia with insulin lispro and regular insulin.<br><br>There was no significant difference in $HbA_{1c}$ (difference, –0.09%; 95% CI, –0.21 to 0.04) or risk of any type of hypoglycemia with insulin aspart and regular insulin.<br><br>Only one trial compared biphasic insulin lispro and biphasic insulin aspart. This study showed no significant difference in $HbA_{1c}$ (difference, 0.14%; 95% CI, –0.02 to 0.30) or overall hypoglycemia in adults with type 2 diabetes. |

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| | | | | Most of the studies with insulin glargine and NPH insulin have allowed the use of oral antidiabetic drugs. Only one study compared insulin glargine and NPH insulin in combination with a prandial insulin without the use of oral antidiabetic drugs. Glycemic control was no better in the insulin glargine group regardless of the type of combined therapy (difference in $HbA_{1c,}$ –0.05%; 95% CI, –0.13 to 0.04, for insulin glargine with oral antidiabetic therapy; 0.28%, 95% CI, 0.07 to 0.49, for insulin glargine with prandial insulin). There was no significant difference in the risk of severe hypoglycemia in the studies that used oral antidiabetic therapy (RR, 0.66; 95% CI, 0.29 to 1.48). The relative risk for nocturnal hypoglycemia significantly favored insulin glargine in both the prandial insulin study (RR, 0.78; 95% CI, 0.62 to 0.98) and the studies that allowed oral antidiabetic drugs (RR, 0.56; 95% CI, 0.47 to 0.68). There was a significant reduction in risk of overall hypoglycemia in favor of insulin glargine in the studies allowing oral antidiabetic therapy but not in the bolus insulin study.<br><br>Most of the studies with insulin detemir and NPH insulin have been conducted in patients receiving oral antidiabetic drugs. One study used prandial insulin (insulin aspart) before meals. There was a significant reduction in $HbA_{1c}$ with NPH insulin compared to insulin detemir in studies that allowed the use of oral antidiabetic drugs (difference, 0.13%; 95% CI, 0.03 to 0.22). The risk for severe hypoglycemia was not statistically significant. The risk for nocturnal hypoglycemia (RR, 0.53; 95% CI, 0.31 to 0.91) and overall hypoglycemia significantly favored insulin detemir.<br><br>There was no significant difference between treatment groups in terms of $HbA_{1c}$ (difference, 0.10%; 95% CI, –0.18 to 0.38) or risk of overall hypoglycemia in the study that used prandial insulin. The risk of nocturnal hypoglycemia was lower in the insulin detemir group (RR, 0.66; 95% CI, 0.45 to 0.96).<br><br>Two studies compared insulin detemir with insulin glargine in patients with type 2 diabetes. One of the studies allowed the use of oral antidiabetic therapy and showed no significant difference in $HbA_{1c}$ |

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| | | | | (difference, 0.10%; 95% CI, –0.06 to 0.26) or nocturnal hypoglycemia. The other study used prandial insulin (insulin aspart) and reported a higher $HbA_{1c}$ with insulin detemir (difference, 0.20%; 95% CI, 0.10 to 0.30). There was no difference in risk of overall hypoglycemia.<br><br>*Pregnant Women With Diabetes*<br>There were no significant differences in $HbA_{1c}$ with insulin lispro or regular insulin (difference, 0.20%; 95% CI, –1.03 to 1.43) or the risk of severe hypoglycemia (RR, 0.21; 95% CI, 0.01 to 4.10) among pregnant women with type 1 diabetes.<br><br>There was no significant difference in $HbA_{1c}$ with insulin lispro or regular insulin (difference, 0.06%; 95% CI, –0.11 to 0.23) among women with gestational diabetes.<br><br>Results from a single trial comparing insulin aspart with regular insulin in pregnant women with type 1 diabetes were similar to those for insulin lispro in terms of $HbA_{1c}$ (difference, –0.08%; 95% CI, –0.28 to 0.12), risk of severe hypoglycemia (RR, 1.14; 95% CI, 0.76 to 1.71) and risk of overall hypoglycemia (RR, 1.04; 95% CI, 0.98 to 1.11).<br><br>Secondary:<br>Not reported |
| **Intermediate-Acting and Long-acting Insulins: Type 1 and 2 Diabetes** | | | | |
| Yenigun et al.[113] (2009)<br><br>Insulin detemir QD<br><br>Patients were originally receiving insulin glargine (QD or BID), and then were switched to insulin detemir. | Subgroup analysis of PREDICTIVE study (MC, OL, OS, PRO)<br><br>Patients with type 1 or 2 diabetes, with or without concomitant oral antidiabetic agents | N=1,285<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Changes in baseline FPG, insulin dose, and body weight; incidence of hypoglycemia; safety | Primary:<br>Switching to insulin detemir significantly decreased $HbA_{1c}$ (insulin glargine QD and type 1 diabetes, -0.47; P<0.0001, insulin glargine QD and type 2 diabetes, -0.51%; P<0.0001, insulin glargine BID and type 1 diabetes; -0.31%; P<0.05, insulin glargine BID and type 2 diabetes; -0.89%; P<0.05).<br><br>Secondary:<br>Significant decreases in self-monitored FPG and within-patient FPG variability were reported in patients who switched from insulin glargine QD to insulin detemir (P<0.000 for all). Results were not significant in patients who switched from insulin glargine BID because of a small sample size. |

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| | | | | Except for type 2 diabetics who switched from insulin glargine BID, total daily insulin dose increased by 1 to 5% in patients transferring to insulin detemir.<br><br>There was a significant decrease in body weight in patients who switched from insulin glargine QD (P<0.05). Body weight decreased in patients who switched from insulin glargine BID; however, it did not reach significance.<br><br>On case of serious hypoglycemia was reported in a patient who switched from insulin glargine QD. No serious adverse events were reported in type 2 diabetes, although three patients experienced major hypoglycemia that were not reported as a severe adverse event. The number of hypoglycemic episodes was significantly reduced in patients with type 1 and 2 diabetes who switched from insulin glargine QD, as well as type 2 diabetes who switched from insulin glargine BID (P<0.0001). There was also a significant decrease in the number of major and nocturnal hypoglycemic events in patients who switched from insulin glargine QD (P<0.0001). |
| **Trials Comparing Insulin Devices** | | | | |
| Ignaut et al.[114] (2009)<br><br>Insulin lispro administered via KwikPen® device<br><br>vs<br><br>insulin lispro administered via vial/syringe<br><br>vs<br><br>insulin aspart administered via | OL, RCT, XO<br><br>Patients 40 to 75 years of age with type 1 or type 2 diabetes who had been preparing and self-injecting insulin using vial and syringe for at least the previous 3 months, and who were pen device-naïve | N=232<br><br>1 day | Primary:<br>Preference (responses to Question 13 of the insulin device preference battery post-assessment and the final preference question)<br><br>Secondary:<br>Characteristics of different insulin pen devices (overall ease of use, ease of | Primary:<br>The KwikPen® was significantly preferred to vial and syringe, with 89% of patients preferring KwikPen® (95% CI, 0.8437-0.9284). KwikPen® was significantly preferred to FlexPen®, with 67% of patients preferring KwikPen® (95% exact CI, 0.6063-0.7312). FlexPen® was significantly preferred to vial and syringe (81%; 95% CI, 0.7529-0.8581).<br><br>Secondary:<br>For the ease of use assessment, 94% of KwikPen® users and 84% of FlexPen® users either strongly agreed or agreed that the device was easy to use (P=0.006).<br><br>For the ease of handling assessment, 87% of KwikPen® users and 73% of FlexPen® users either strongly agreed or agreed that the pen was easy to hold in their hand when they injected insulin (P=0.002).<br><br>For the ease of injection assessment, 85% of KwikPen® users and 66% of |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| FlexPen® device | | | handling, ease of pressing injection button while injecting) | FlexPen® users either strongly agreed or agreed that the injection buttons on their respective pens were easy to press when injecting their dose (P<0.001).<br><br>When comparing preference with the KwikPen® to vial/syringe, all comparison were statistically significant favoring KwikPen® in terms of appearance, quality of the device, discretion, convenience, use in public, easy to learn, easy to use, reliability, dose confidence, ability to follow an insulin regimen, overall satisfaction, and recommendation to others. |
| Korytkowski et al.[115] (2003)<br><br>Insulin aspart protamine and insulin aspart 70/30 mix vial/syringe for 4 weeks<br><br>vs<br><br>biphasic insulin aspart protamine and insulin aspart 70/30 mix prefilled pen for 4 weeks | OL, RCT, XO<br><br>Patients with type 1 diabetes and type 2 diabetes were stabilized on 70% insulin aspart and 30% insulin aspart protamine then randomized to use vial/syringe or a prefilled pen for 4 weeks; after 4 weeks, patients were XO to the other administration method; baseline $HbA_{1c}$ 8.7% | N=121<br><br>12 weeks | Primary:<br>Patient preference<br><br>Secondary:<br>Effect on glycemic control ($HbA_{1c}$, FPG, fructosamine, and four-point glucose profile) | Primary:<br>Seventy-four percent indicated preference for prefilled pen over the vial/syringe (95% CI, 71 to 87) compared to 20% who indicated a preference for the vial/syringe.<br><br>Secondary:<br>Overall, a significant reduction in $HbA_{1c}$ (-3%; P<0.05) was observed during the entire study (no comparison between treatment groups made).<br><br>There was no significant difference in FPG, fructosamine or four-point glucose profile between treatment groups.<br><br>There was no difference in safety profile between treatment groups. |
| **Insulin Therapy Compared to Other Antidiabetic Medications: Type 2 Diabetes** | | | | |
| Mu et al.[116] (2012)<br><br>Insulin glargine<br><br>vs<br><br>no additional treatment | RCT<br><br>Patients 35 to 50 years of age with newly diagnosed type 2 diabetes, FPG ≥9.0 mmol/L, and $HbA_{1c}$ ≥9.0% | N=129<br><br>1 year | Primary:<br>Effects on β-cell function, diabetes remission rate<br><br>Secondary:<br>Not reported | Primary:<br>Both treatment groups improved HOMA-B and HOMA-IR significantly. They had similar effects on insulin resistance (0.50±0.09 vs 0.48±0.09; P=0.23). However, the addition of insulin therapy could recover β-cell function much more than no additional treatment (2.17±0.14 vs 2.11±0.13; P=0.03).<br><br>More patients achieved target glycemic control with the addition of insulin therapy (98.3% [58 of 59]) in less time (10.4±2.5 days) compared to no |

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| All patients received oral antidiabetic medications.<br><br>Active treatments were stopped after normoglycemia was maintained for 3 months.<br><br>Patients were then followed-up with diet and physical exercise at 1 year. | | | | additional treatment (95.7% [67 of 70] and 12.4±3.4 days). At one year follow-up, more patients maintained target glycemia without any drugs in patients who received additional insulin therapy compared to patients who received no additional treatment (37.9 vs 20.9%).<br><br>Secondary:<br>Not reported |
| Okerson et al.[117] (2010)<br><br>Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID<br><br>vs<br><br>placebo or insulin<br><br>All patients also received existing antidiabetic treatment regimens. | Post-hoc analysis (6 RCTs)<br><br>Type 2 diabetics ≥18 years of age with $HbA_{1c}$ ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m$^2$, and stable body weight | N=2,171<br><br>24 to 52 weeks | Primary:<br>Change in baseline BP and pulse pressure<br><br>Secondary:<br>Not reported | Primary:<br>In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, -2.80±0.75 mm Hg; P=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; P=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; P=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported).<br><br>Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001).<br><br>By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of "abnormal DBP" to "normal DBP" compared to placebo (treatment difference, 41.4 vs 32.4%; P=0.02).<br><br>Secondary:<br>Not reported |
| Diamant et al.[118] (2010)<br>DURATION-3<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>insulin glargine SC QD<br><br>All patients received existing background oral glucose-lowering regimens. | OL, PG, RCT<br><br>Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, $HbA_{1c}$ 7.1 to 11.0%, BMI 25 to 45 kg/m$^2$, and a stable body weight ≥3 months | N=456<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell | Primary:<br>Decreases in $HbA_{1c}$ were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, $HbA_{1c}$ was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; P=0.031).<br><br>Secondary:<br>Significantly greater proportions of exenatide ER-treated patients achieved $HbA_{1c}$ <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients.<br><br>Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; P=0.001).<br><br>With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | function, insulin profile, patient-reported quality of life, safety | (P<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (P=0.022) and before breakfast (P<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (P=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (P=0.001) and evening meals (P=0.033).<br><br>Seventy nine percent of patients receiving exenatide ER experienced both a decrease in $HbA_{1c}$ and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in $HbA_{1c}$ and increase in body weight.<br><br>Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; P<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed.<br><br>Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; P<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; P<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed.<br><br>Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients). |
| Diamant et al.[119] (2012)<br>DURATION-3<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>insulin glargine SC QD<br><br>All patients received existing background oral glucose-lowering regimens. | ES<br><br>Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, $HbA_{1c}$ 7.1 to 11.0%, BMI 25 to 45 kg/m$^2$, and a stable body weight ≥3 months | N=390<br><br>84 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportions of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety | Primary:<br>At 84 weeks, $HbA_{1c}$ decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (P=0.029).<br><br>Secondary:<br>The proportions of patients who achieved end point $HbA_{1c}$ targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (P=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (P=0.009), respectively.<br><br>Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (P<0.001).<br><br>Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001).<br><br>Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine. |
| Bergenstal et al.[120] (2009)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID<br><br>vs<br><br>insulin aspart 12 units QD before | OL, PG, RCT<br><br>Patients 18 to 80 years of age with type 2 diabetes mellitus and $HbA_{1c}$ ≥8.0%, insulin-naïve, and receiving treatment with metformin and a sulfonylurea for at | N=372<br><br>24 Weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>FPG, eight-point plasma glucose profiles, changes in body weight | Primary:<br>At 24 weeks, $HbA_{1c}$ values were 7.61, 7.75, 8.46% for BIAsp 30 BID, BIAsp 30 QD, and exenatide, respectively (both P<0.0001 compared to exenatide).<br><br>At the end of the study, 37% of patients in the BIAsp 30 BID group achieved an $HbA_{1c}$ <7.0% compared to 20% of patients in the exenatide group (P=0.0060). Additionally, 25% of patients in the BIAsp 30 BID group achieved an $HbA_{1c}$ ≤6.5% compared with 8% in the exenatide group (P=0.0004). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| dinner (BIAsp 30 QD)<br><br>vs<br><br>insulin aspart 12 units divided equally before breakfast and dinner (BIAsp 30 BID)<br><br>All patients were receiving metformin with or without a sulfonylurea.<br><br>Insulin dose was titrated as necessary. | least 3 months prior to enrolling in the study | | | At the end of the study, 26% of patients in the BIAsp 30 QD group achieved an $HbA_{1c}$ <7.0% compared to 20% of patients in the exenatide group (P=0.3488). Additionally, 12% of patients in the BIAsp 30 QD group achieved an $HbA_{1c}$ ≤6.5% compared with 8% in the exenatide group (P=0.3802).<br><br>The percentage of patients who achieved $HbA_{1c}$ ≤6.5% was higher with BIAsp 30 BID compared to BIAsp 30 QD (25 vs 12%; P=0.0122).<br><br>Secondary:<br>There were significant changes in FPG with BIAsp 30 BID (-62.7 mg/dL; P<0.0001 vs exenatide) and BIAsp 30 QD (-52.4 mg/dL; P=0.0002 vs exenatide) compared to exenatide (-21.4 mg/dL).<br><br>At the end of the study, the eight-point plasma glucose profiles were significantly lower with BIAsp 30 BID and BIAsp 30 QD than exenatide.<br><br>At 24 weeks, hypoglycemia was reported in 56% of patients in the BIAsp 30 QD group, 61% of patients in the BIAsp 30 BID group, and 29% in the exenatide group.<br><br>Weight loss was reported in the exenatide group (-1.9 kg) compared with weight gain in the BIAsp 30 QD (+2.8 kg) and BIAsp 30 BID (4.1 kg).<br><br>There were more reports of nausea and vomiting with exenatide than in the insulin groups. |
| Heine et al.[121] (2005)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID<br><br>vs<br><br>insulin glargine QD at bedtime | OL, RCT<br><br>Patients 30 to 75 years of age with type 2 diabetes not adequately controlled (defined as $HbA_{1c}$ 7.0 to 10.0%) with combination metformin and | N=551<br><br>26 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Change in FPG, fasting glucose <100 mg/dL and body weight loss | Primary:<br>At 26 weeks, similar reductions in $HbA_{1c}$ were noted between exenatide and insulin glargine (–1.11%; CI, –0.123 to 0.157).<br><br>Secondary:<br>A significantly reduction in fasting plasma glucose from baseline was observed in the insulin glargine group (–51.5 mg/dL; P<0.001). The reduction from baseline in the exenatide group was not significant (–25.7 mg/dL). A significant reduction was observed in the insulin group when compared to the exenatide group (95% CI, 20 to 34 mg/dL). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| All patients were receiving existing metformin and/or sulfonylurea regimens. | sulfonylurea therapy at maximally effective doses, BMI between 25 to 45 kg/m$^2$ and a history of stable body weight (≤10% variation for ≥3 months before screening) | | | A significantly greater proportion of patients taking insulin glargine (21.6%) achieved fasting glucose of <100 mg/dL than those taking exenatide (8.6%; P<0.001).<br><br>A significant weight loss was experienced in the exenatide group (–2.3 kg) compared to a gain of +1.8 kg in the insulin group (CI, –4.6 to –3.5; P<0.001).<br><br>Similar rates of hypoglycemia were reported with both agents (CI, –1.3 to 3.4 events/patient-year). Exenatide patients had a higher incidence of daytime hypoglycemia (CI, 0.4 to 4.9 events/patient-year), and a lower rate of nocturnal hypoglycemia than insulin glargine patients (CI, –2.3 to –0.9 events/patient-year).<br><br>A significantly higher incidence of gastrointestinal side effects, including nausea (57.1 vs 8.6%; P<0.001), vomiting (17.4 vs 3.7%; P<0.001) and diarrhea (8.5 vs 3%; P=0.006), upper abdominal pain (P=0.012), constipation (P=0.011), dyspepsia (P=0.011), decreased appetite (P=0.021), and anorexia (P=0.002) were reported in the exenatide group vs the insulin group.<br><br>Withdrawals due to adverse events occurred in 9.5% of exenatide patients vs 0.7% of insulin patients. |
| Secnik Boye et al.[122] (2006)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID<br><br>vs<br><br>insulin glargine QD at bedtime<br><br>All patients were | MC, OL, RCT<br><br>Secondary analysis on patients with type 2 diabetes inadequately controlled (defined as an $HbA_{1c}$ between 7.0 and 10.0%) with sulfonylurea and metformin therapy at maximally effective doses, enrolled in a previous 26 week | N=455<br><br>26 weeks | Primary:<br>Patient-reported health outcome measures: Diabetes Symptom Checklist-revised, DTSQ, EQ-5D, Medical Outcomes Study 36-Item Short-Form Health Survey, Diabetes Medical Outcomes Study 36-Item Short-Form Health | Primary:<br>Both exenatide and insulin glargine groups experienced a significant improvement from baseline in patient-reported health outcome measures as demonstrated by Diabetes Symptom Checklist-revised overall scores, DTSQ, EQ-5D and Medical Outcomes Study 36-Item Short-Form Health Survey scores (P<0.05 for all measures). There was not a statistical difference between treatment groups in any of the outcome measures (P>0.05 for all measures).<br><br>Neither the exenatide nor the insulin glargine group experienced a significant improvement in Medical Outcomes Study 36-Item Short-Form Health Survey scores (P=0.93 for both groups).<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| receiving existing metformin and/or sulfonylurea regimens. | study | | Survey<br><br>Secondary:<br>Not reported | Not reported |
| Nauck et al.[123] (2007)<br><br>Exenatide 5 µg BID for 4 weeks, then 10 µg BID<br><br>vs<br><br>insulin aspart BID<br><br>All patients were receiving existing metformin and/or sulfonylurea regimens. | MC, OL, RCT<br><br>Patients 30 and 75 years of age who had suboptimal glycemic control despite receiving optimally effective metformin and sulfonylurea therapy for ≥3 months, $HbA_{1c}$ ≥7.0 and ≤11.0%, a BMI ≥25 and ≤40 kg/m$^2$, and a history of stable body weight (≤10% variation for ≥3 months) | N=501<br><br>52 weeks | Primary:<br>Mean change in $HbA_{1c}$ levels, weight, fasting serum glucose levels, postprandial glucose levels, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>There was not a significantly different change from baseline in mean $HbA_{1c}$ levels between the exenatide (–1.04%) and insulin aspart groups (–0.89%, 95% CI, −0.32% to 0.01%; P=0.067).<br><br>Patients in the exenatide group experienced a gradual weight loss of –2.5 kg, compared to a gradual weight gain of 2.9 kg in the insulin aspart group, (95% CI, −5.9 to −5.0; P<0.001) at the end of 52 weeks.<br><br>Patients in both exenatide (–1.8 mmol/L) and insulin aspart (–1.7 mmol/L) groups had a significant decrease in fasting serum glucose compared to baseline (P<0.001 for both groups). There was not a significant difference between groups (CI, −0.6 to 0.4; P=0.689).<br><br>Patients in the insulin aspart group had significantly lower mean glucose values at pre-breakfast (P=0.037), pre-lunch (P=0.004) and 03.00 hours (P=0.002). Patients in the exenatide group had a greater reduction in postprandial glucose excursions following morning (P<0.001), midday (P=0.002) and evening meals (P<0.001).<br><br>The withdrawal rate was 21.3% in the exenatide group and 10.1% in the insulin aspart group. Adverse events that were more commonly reported in the exenatide vs insulin aspart group included: nausea (33.2 vs 0.4%), vomiting (15.0 vs 3.2%), diarrhea (9.5 vs 2%) and other clinically relevant adverse events (13.4 vs 6.4%).<br><br>Secondary:<br>Not reported |
| Kabadi et al.[124] (2003)<br><br>Tolazamide 1 gram daily plus premixed | PC, RCT<br><br>Patients with type 2 diabetes mellitus with a lapse of | N=40<br><br>7 months | Primary:<br>Changes in body weight, $HbA_{1c}$, and fasting C-peptide concentrations | Primary:<br>Changes in body weight were 2.5±0.8 kg for the tolazamide group, 2.6±1.0 kg for the glyburide group, 2.4±0.9 kg for the glipizide XL group, and 2.2±0.7 kg for the glimepiride group, all were significant compared to placebo (P<0.01) after the addition of insulin. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| 70% NPH and 30% regular insulin daily<br><br>vs<br><br>glyburide 20 mg daily plus premixed 70% NPH and 30% regular insulin daily<br><br>vs<br><br>glipizide XL plus premixed 70% NPH and 30% regular insulin daily<br><br>vs<br><br>glimepiride 8 mg daily plus premixed 70% NPH and 30% regular insulin daily<br><br>vs<br><br>placebo plus premixed 70% NPH and 30% regular insulin daily | glycemic control, established by documentation of $HbA_{1c}$ >7.4% on ≥2 occasions at an interval of ≥3 months in each patient while taking oral sulfonylureas consisting of one of these drugs in the maximum recommended daily dose: tolazamide 1 g daily, glyburide 20 mg daily, glipizide XL 20 mg daily, or glimepiride 8 mg daily | | Secondary:<br>Changes in daily insulin dose and the number of hypoglycemic episodes confirmed by finger stick blood glucose <60 mg/ dL | All groups achieved optimal glycemic control as expressed by $HbA_{1c}$ <7.4%, 1% above the highest normal level of 6.4% in our laboratory as recommended by the American Diabetes Association after the addition of insulin. $HbA_{1c}$ was 6.8±0.4% for tolazamide, 6.9±0.4% for glyburide, 6.7±0.4% for glipizide XL, 6.7±0.3% for glimepiride, and 7.0±0.3% for placebo.<br><br>C-peptide levels decreased in all groups. The reduction in the C-peptide level was significantly greater (P<0.05) in the placebo group compared to the sulfonylurea groups. There were no significant differences among the sulfonylurea groups.<br><br>Secondary:<br>Patients receiving sulfonylureas required a significantly lower (P<0.01) daily insulin dose, as well as dose per kilogram of body weight in comparison to patients receiving placebo (P<0.01).<br><br>The daily insulin dose and units per kilogram of body weight was significantly lower (P<0.05) in patients receiving glimepiride in comparison to those receiving tolazamide, glyburide, or glipizide XL.<br><br>The number of hypoglycemic episodes during the last four weeks of the study were significantly lower in the sulfonylurea groups as compared to the placebo group (P<0.01). The differences among the individual sulfonylurea groups were not significantly different. |
| Russell-Jones et al.[125]<br>(2009)<br>LEAD-5<br><br>Liraglutide 1.8 mg SC QD | PC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥3 | N=581<br><br>26 weeks | Primary:<br>Change in baseline in $HbA_{1c}$<br><br>Secondary:<br>Change in baseline body | Primary:<br>Decreases in $HbA_{1c}$ were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015). |

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| vs<br><br>placebo<br><br>vs<br><br>insulin glargine (OL)<br><br>All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day. | months before screening, $HbA_{1c}$ 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m$^2$ | | weight, waist circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP | Secondary:<br>The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001).<br><br>The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608).<br><br>Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported).<br><br>Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported).<br><br>Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide.<br><br>A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; |

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| | | | | P=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin. |
| Civera et al.[126] (2008)<br><br>Repaglinide 2 mg TID before meals plus metformin 850mg BID plus NPH insulin before dinner<br><br>vs<br><br>metformin 850mg BID plus NPH insulin before dinner<br><br>vs<br><br>NPH insulin BID | OL, PG<br><br>Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs | N=37<br><br>24 weeks | Primary:<br>$HbA_{1c}$, hypoglycemia, body weight<br><br>Secondary:<br>Not reported | Primary:<br>The $HbA_{1c}$ was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02).<br><br>The absolute reduction in $HbA_{1c}$ was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and<br>-1.4% in the insulin NPH group.<br><br>Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01).<br><br>Significant differences in weight gain and hypoglycemia were not seen.<br><br>Secondary:<br>Not reported |
| Cesur et al.[127] (2007)<br><br>Repaglinide up to 4 mg QD<br><br>vs<br><br>glimepiride up to 8 mg QD<br><br>vs<br><br>insulin glargine up to 36 U QD | MC, OL, OS, PRO<br><br>Patient 33 to 67 years of age with type 2 diabetes, $HbA_{1c}$ 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month | N=65<br><br>Duration not specified | Primary:<br>FBG, PPG, $HbA_{1c}$, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramandan fasting<br><br>Secondary:<br>Not reported | Primary:<br>In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan.<br><br>In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods).<br><br>There was no significant change in $HbA_{1c}$ levels between the nonfasting and fasting groups.<br><br>There was a significant increase in fructosamine levels in both fasting |

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| | | | | group and non-fasting group at one-month post-Ramadan (P<0.01 for both).<br><br>BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and post-Ramadan in nonfasting group).<br><br>TC, LDL-C and TG did not change throughout the study period but HDL-C levels significantly increased at post-Ramadan in the fasting group (P<0.01). In nonfasting group, LDL-C and TG levels significantly increased at post-Ramadan (P<0.05 for both).<br><br>At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia.<br><br>Secondary:<br>Not reported |
| Chisalita et al.[128] (2009)<br><br>Repaglinide 4mg TID before meals for 10 weeks<br><br>vs<br><br>insulin aspart 13 to 46 units/day (4 to 20 units at breakfast, 5 to 15 units at lunch and 4 to 15 units at dinner) for 10 | XO<br><br>Patients ≥60 years of age with type 2 diabetes | N=5<br><br>20 weeks | Primary:<br>$HbA_{1c}$, blood glucose, C-peptide, free human insulin, free total (human and analogue) insulin, proinsulin, islet amyloid polypeptide, growth hormone binding protein, and plasma lipoprotein concentrations were measured | Primary:<br>The $HbA_{1c}$ was 6.1% at the end of repaglinide therapy and 5.9% at the end of insulin aspart therapy (P=NS).<br><br>C-peptide concentrations were significantly higher during repaglinide treatment compared to insulin aspart treatment (AUC 2,453 vs 1,153; P=0.02).<br><br>Free human insulin levels were significantly higher on repaglinide than on insulin aspart therapy (AUC 215 vs128; P<0.05).<br><br>Proinsulin levels were higher when measured during repaglinide treatment than during treatment with insulin aspart.<br><br>Islet amyloid polypeptide levels tended to be higher during repaglinide compared to insulin aspart treatment (P=NS). |

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| weeks | | | Secondary:<br>Not reported | Fasting plasma insulin like growth factor-I concentration was 220 ng/mL during treatment with insulin aspart and 226 ng/mL during treatment with repaglinide (P=NS).<br><br>Compared to fasting levels, the insulin like growth factor binding protein-1 levels were lower during repaglinide (P<0.05), but not during insulin aspart treatment (P=NS).<br><br>Repaglinide treatment increased plasma growth hormone binding protein concentration compared with insulin aspart (1,094 vs 942 pmol/L; P=0.02).<br><br>Repaglinide treatment resulted in higher postprandial plasma TC, TG and apolipoprotein B concentrations compared with insulin aspart. There was no significant difference in LDL-C or HDL-C<br><br>Secondary:<br>Not reported |
| Meneghini et al.[129] (abstract). (2010)<br><br>Insulin glargine<br><br>vs<br><br>pioglitazone | MC, OL, PG<br><br>Adults with poorly controlled type 2 diabetes ($HbA_{1c}$ 8.0 to 12.0%), despite ≥3 months of sulfonylurea or metformin monotherapy | N=389<br><br>48 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, BMI, body weight, safety | Primary:<br>At trial end, insulin glargine resulted in a significantly greater reduction in $HbA_{1c}$ compared to pioglitazone (-2.48 vs -1.86%; 95% CI, -0.93 to -0.31; P=0.001).<br><br>Secondary:<br>Insulin glargine resulted in significantly greater reductions in FPG at all time points (trial end difference, -34.9 mg/dL; 95% CI, -47.6 to -22.2; P<0.0001).<br><br>Changes in weight and BMI were similar between the two treatments.<br><br>Compared to pioglitazone, insulin glargine resulted in a lower overall incidence of possibly treatment-emergent adverse events (12.0 vs 20.7%) and fewer study discontinuations (2.2 vs 9.1%), but a higher rate (per patient-year) of confirmed clinically relevant hypoglycemic episodes (4.97 vs 1.04; P<0.0001) and severe hypoglycemia (0.07 vs 0.01; P=0.0309). |
| Dorkhan et al.[130] | RCT, OL | N=36 | Primary: | Primary: |

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| (2008)<br><br>Pioglitazone 30 to 45 mg QD and existing oral hypoglycemic therapy<br><br>vs<br><br>insulin glargine 6-10 IU/day administered in the morning (titrated as necessary) and existing oral hypoglycemic therapy | Patients with type 2 diabetes and inadequate glycemic control (defined as treatment with metformin and sulfonylurea/ meglitinide in doses ≥50% of maximum recommended doses and $HbA_{1c}$ >6.2% | 26 weeks | Change in $HbA_{1c}$, β-cell function, insulin sensitivity, degree of patient satisfaction<br><br>Secondary:<br>Not reported | After 26 weeks, the change in $HbA_{1c}$ from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050).<br><br>There was no difference in insulin, β-cell function, or insulin sensitivity among the two treatment groups (P value not significant). Insulin glargine resulted in a greater reduction in proinsulin concentrations than pioglitazone (-55 vs -25%; P<0.01).<br><br>Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P value not significant).<br><br>The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups.<br><br>There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups).<br><br>Secondary:<br>Not reported |
| Aljabri et al.[131] (2004)<br><br>Pioglitazone 30 to 45 mg QD<br><br>vs<br><br>NPH insulin 0.3 unit/kg QD<br><br>All patients were receiving existing sulfonylurea or | OL, RCT<br><br>Patients with poorly controlled type 2 diabetes ($HbA_{1c}$ >8%) with insulin secretagogues and metformin monotherapy | N=62<br><br>16 weeks | Primary:<br>Effect on $HbA_{1c}$, FPG, incidence of hypoglycemia (< 68 mg/dL), effect on lipoproteins, quality of life (assessed using the DTSQ)<br><br>Secondary:<br>Not reported | Primary:<br>Similar reductions in $HbA_{1c}$ were observed in pioglitazone-treated (–1.9%) and NPH insulin-treated patients (–2.3%; P=0.32).<br><br>Nonsignificant differences in reduction in FPG were observed with NPH insulin (–77 mg/dL) and pioglitazone (–52 mg/dL; P=0.07).<br><br>Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02).<br><br>Significant increases in HDL-C were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02).<br><br>No significant differences in total cholesterol, LDL cholesterol and |

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| metformin therapy | | | | triglycerides were reported between the two treatment groups.<br><br>No significant differences were noted for the DTSQ scores between the two treatment groups.<br><br>Secondary:<br>Not reported |
| Ligvay et al.[132] (2009)<br><br>Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID<br><br>vs<br><br>insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily<br><br>All patients were receiving metformin 1,000 mg BID<br><br>Doses of medications could be titrated at the investigator's discretion. | RCT, OL<br><br>Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve | N=58<br><br>36 months | Primary:<br>$HbA_{1c}$, rate of treatment failures (defined as $HbA_{1c}$ >8.0%), hypoglycemia, weight gain, compliance, QOL, and patient satisfaction<br><br>Secondary:<br>Not reported | Primary:<br>After 36 months, $HbA_{1c}$ was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26).<br><br>The percentage of patients achieving $HbA_{1c}$ <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the $HbA_{1c}$ goal at the end of 36 months.<br><br>Three patients in each group reached the "treatment failure" end point.<br><br>The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53).<br><br>In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04).<br><br>Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group.<br><br>There were differences between the groups for any of the 12 QoL domains evaluated.<br><br>All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization.<br><br>Secondary: |

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| | | | | Not reported |
| Nichols et al.[133] (2007)<br><br>Metformin<br><br>vs<br><br>sulfonylurea<br><br>vs<br><br>insulin<br><br>vs<br><br>TZDs | MC, OS, RETRO<br><br>Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies | N=9,546<br><br>≥12 months | Primary:<br>Weight changes<br><br>Secondary:<br>Not reported | Primary:<br>Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.<br><br>Secondary:<br>Not reported |
| Black et al.[134] (2007)<br><br>Meglitinide<br><br>vs<br><br>meglitinide plus metformin<br><br>vs<br><br>meglitinide plus insulin<br><br>vs<br><br>metformin<br><br>vs | MA (15 trials)<br><br>Patients with type 2 diabetes | N=3,781<br><br>Duration varied | Primary:<br>Mortality and morbidity<br><br>Secondary:<br>Change in $HbA_{1c}$, weight or BMI, hypoglycemia, adverse effects, quality of life | Primary:<br>No trials reported the effect of meglitinides on mortality and morbidity.<br><br>Secondary:<br>In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in $HbA_{1c}$ (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in $HbA_{1c}$ was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in $HbA_{1c}$ compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in $HbA_{1c}$ compared to metformin.<br><br>Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin.<br><br>Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides. |

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| placebo | | | | There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes.<br><br>There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization DTSQ improved significantly in patients receiving repaglinide compared to patients receiving placebo. |
| Saenz et al.[135] (2005)<br><br>Metformin monotherapy<br><br>vs<br><br>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin | MA (29 RCTs)<br><br>Adult patients with type 2 diabetes | N=5,259<br><br>≥3 months | Primary:<br>Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photo-coagulation, blindness in one eye, or cataract extraction); diabetes-related | Primary:<br>Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide†, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).<br><br>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02).<br><br>Secondary:<br>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for $HbA_{1c}$ when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas. |

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| | | | death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality<br><br>Secondary: Changes in $HbA_{1c}$, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow | |
| Monami et al.[136] (2011)<br><br>DPP-4 inhibitors (linagliptin, alogliptin*, sitagliptin, saxagliptin, vildagliptin*)<br><br>vs<br><br>placebo or active comparator (oral hypoglycemic agents and/or insulin) | MA (53 trials)<br><br>Patients with type 2 diabetes who were receiving a DPP-4 inhibitor | N=33,881<br><br>≥24 weeks | Primary: Incidence of cancer<br><br>Secondary: Incidence of pancreatitis, all-cause and cardiovascular mortality, incidence of major cardiovascular events | Primary: There were 176 cases of cancer (107 and 69 in patients receiving DPP-4 inhibitors and comparators, respectively); 12.5% were gastrointestinal, 5.7% were pancreatic, 6.2% were pulmonary, 14.7% were mammary gland/female genital tract, 11.3% were male urogenital tract, 3.4% were thyroid, and 26.1% were of another origin. There was no difference in the proportion of cases between patients receiving DPP-4 inhibitors or a comparator (P=0.90).<br><br>Secondary: The risk of pancreatitis with DPP-4 inhibitors was 0.786 (P=0.55).<br><br>The number of reported deaths was 28 and 31 with DPP-4 inhibitors and comparators, respectively. Cardiovascular deaths occurred in 10 patients receiving DPP-4 inhibitors and 20 patients receiving comparators. The risk for all-cause death and cardiovascular death in patients receiving DPP-4 inhibitors was 0.668 (P=0.149 and P=0.054, respectively). |

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| | | | | There were 137 and 120 major cardiovascular events reported with DPP-4 inhibitors and comparators, respectively. DPP-4 inhibitors were associated with a significantly lower risk of major cardiovascular events (OR, 0.689; P=0.006). |
| Shyangdan et al.[137] (2011)<br><br>GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)<br><br>vs<br><br>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas) | MA (RCTs)<br><br>Type 2 diabetics ≥18 years of age | N=not reported<br><br>8 to 26 weeks | Primary:<br>Change in baseline $HbA_{1c}$, incidence of hypoglycemia, weight change<br><br>Secondary:<br>Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function | Primary:<br>Change in baseline $HbA_{1c}$<br>Exenatide ER significantly decreased $HbA_{1c}$ compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an $HbA_{1c}$ <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an $HbA_{1c}$ <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).<br><br>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased $HbA_{1c}$ (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in $HbA_{1c}$ compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).<br><br>Compared to placebo, liraglutide 1.8 mg significantly decreased an $HbA_{1c}$ (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide |

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| | | | | 1.8 mg were more likely to achieve $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in $HbA_{1c}$ compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).<br><br>Liraglutide decreased $HbA_{1c}$ to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).<br><br>Liraglutide 1.2 mg was associated with a non-significant increase in $HbA_{1c}$ compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an $HbA_{1c}$ <7.0% compared to the 1.8 mg dose (P=0.92).<br><br>Incidence of hypoglycemia<br>The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).<br><br>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).<br><br>Weight loss<br>Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).<br><br>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).<br><br>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).<br><br>Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).<br><br>Secondary:<br>Data on mortality and morbidity were not reported for any treatment.<br><br>Quality of life<br>Exenatide ER significantly improved weight-related QOL and IWQOL |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.<br><br>Data for liraglutide were not reported.<br><br>Safety<br>Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).<br><br>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.<br><br>BP<br>There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.<br><br>FPG<br>There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).<br><br>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).<br><br>PPG<br>There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).<br><br>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Lipid profile<br>TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.<br><br>β cell function<br>Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio. |
| Gangji et al.[138] (2007)<br><br>Glyburide<br><br>vs<br><br>sulfonylureas, meglitinides, insulin | MA (21 trials)<br><br>Patients with type 2 diabetes | N=not reported<br><br>Duration varied | Primary:<br>Hypoglycemia, glycemic control, cardiovascular events, body weight, death<br><br>Secondary:<br>Not reported | Primary:<br>Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52; 95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49).<br><br>Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues.<br><br>Secondary:<br>Not reported |
| Lincoff et al.[139] (2007)<br><br>Pioglitazone | DB, MA, RCT with placebo or active comparator | N=16,390 (19 trials)<br><br>4 months to | Primary:<br>Composite of death from any cause, MI or stroke | Primary:<br>Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| monotherapy vs metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial)<br><br>or<br><br>pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo | Adult patients with type 2 diabetes and inadequate glycemic control | 3.5 years | Secondary:<br>Incidence of serious heart failure | Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09).<br><br>Progressive separation of time-to-event curves became apparent after approximately one year of therapy.<br><br>Secondary:<br>Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17). |
| Karter et al.[140] (2005)<br><br>Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies | Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001 | N=23,440<br><br>10.2 months (mean) | Primary:<br>Time-to-incident admission to hospital for congestive heart failure<br><br>Secondary:<br>Not reported | Primary:<br>Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99).<br><br>Secondary:<br>Not reported |
| Nissen et al.[141] (2007)<br><br>Rosiglitazone | MA of RCTs of more than 24 weeks that had outcome data for MI and | 42 trials<br><br>n=15,560 for rosiglitazone; | Primary:<br>MI and death from cardiovascular causes | Primary:<br>Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| monotherapy or combination therapy<br><br>vs<br><br>placebo or active comparators (including gliclazide*, glimepiride, glipizide, glyburide, insulin, and metformin) | death from cardiovascular causes (included ADOPT and DREAM trials)<br><br>Mean age of participants was 56 years, mean baseline $HbA_{1c}$ 8.2% | n=12,283 for comparator<br><br>24 to 208 weeks | Secondary:<br>Not reported | Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06).<br><br>Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24).<br><br>Secondary:<br>Not reported |
| **Long-Term Outcomes Trials** | | | | |
| DCCT Research Group[142] (1993)<br><br>Insulin administered QD or BID<br><br>vs<br><br>insulin administered TID or via external pump | RCT<br><br>Insulin-dependent patients with type 1 diabetes with mild retinopathy (secondary prevention cohort) or without retinopathy (primary prevention cohort), baseline $HbA_{1c}$ 9.1% in both treatment groups | N=1,441<br><br>6.5 years (mean) | Primary:<br>Effect on retinopathy development (primary prevention cohort) or progression (secondary prevention cohort)<br><br>Secondary:<br>Effect on renal function (micro-albuminuria and albuminuria), neuropathy development, and macrovascular disease | Primary:<br>Intensive insulin therapy significantly reduced the risk of retinopathy onset (primary prevention cohort) by 76% compared to standard therapy (P<0.001).<br><br>Intensive insulin therapy significantly reduced the risk of retinopathy progression (secondary prevention cohort) by 54% compared to standard therapy (P<0.001).<br><br>Secondary:<br>Intensive insulin therapy significantly reduced the risk of microalbuminuria by 34% in the primary prevention cohort (P=0.04) and by 43% in the secondary prevention cohort (P=0.001) compared to standard therapy.<br><br>Intensive insulin therapy significantly reduced the risk of albuminuria by 56% in the secondary prevention cohort (P=0.01) compared to standard therapy.<br><br>Intensive insulin therapy significantly reduced the risk of neuropathy appearance by 69% in the primary prevention cohort (P=0.006) and by 57% in the secondary prevention cohort (P<0.001) compared to standard |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | therapy.<br><br>Nonsignificant reduction of risk of macrovascular disease was observed with intensive insulin therapy (44%; 95% CI, -10 to 68) compared to standard therapy.<br><br>Intensive insulin therapy had a threefold higher incidence of hypoglycemic events (P<0.001) compared to standard therapy. |
| UKPDS Group[143] (1998)<br><br>Intensive therapy with sulfonylurea (chlorpropamide, glyburide, or glipizide) or insulin<br><br>vs<br><br>dietary therapy | RCT<br><br>Patients newly diagnosed with type 2 diabetes, baseline $HbA_{1c}$ 7.05% in the dietary treatment group and 7.09% in the intensive therapy group | N=3,867<br><br>10 years | Primary:<br>Time to the first occurrence of any diabetes-related endpoint, time to diabetes-related death, all-cause mortality<br><br>Secondary:<br>MI, sudden death, stroke, amputation or death due to peripheral vascular disease, microvascular complications, retinopathy, vitreous hemorrhage, and/or fatal or nonfatal renal failure | Primary:<br>There was a 12% risk reduction (95% CI, 1 to 21; P=0.029) for any diabetes-related end point, 10% risk reduction (95% CI, -11 to 27; P=0.34) for any diabetes-related death, and a 6% risk reduction (95% CI, -10 to 20; P=0.44) for all-cause mortality when intensive therapy (sulfonylurea or insulin) was compared to conventional therapy with diet.<br><br>Patients receiving an intensive treatment (sulfonylurea or insulin) had a 25% risk reduction (95% CI, 7 to 40; P=0.0099) in microvascular end points compared with conventional therapy with diet. Most of this reduction was due to fewer cases of retinal photocoagulation.<br><br>There were no differences between the intensive and conventional treatment groups or between the three intensive treatment groups in the number of patients who had a silent MI, cardiomegaly, evidence of peripheral vascular disease, or absent peripheral pulses.<br><br>Secondary:<br>There was no significant difference between chlorpropamide, insulin, and glibenclamide in macrovascular events.<br><br>There was no significant difference between the three intensive treatments in microvascular end points or in the risk reduction for retinal photocoagulation. |

*Agent is not available in the United States.
†Glibenclamide is a synonym for glyburide.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily, QID=four times daily
Study abbreviations: AC=active-comparator, CS=comparator study, ES=extension study, MA=meta analysis, MC=multicenter, MN=multinational, NI=noninferiority, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, SR=systematic review, XO=cross-over

Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, CSII=continuous subcutaneous insulin infusion, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, $HbA_{1c}$=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HR=hazard ratio, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=human insulin isophane (neutral protamine Hagedorn), OR=odds ratio, PP=per protocol, PPG=post-prandial glucose, REG=regular human insulin, RR=relative risk, SBP=systolic blood pressure, SDS=standard deviation score, SEM=standard error of mean, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione, WMD=weighted mean difference

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
Yamada et al. evaluated the effects of switching patients to biphasic insulin lispro. Patients with type 2 diabetes who were receiving biphasic human insulin (70/30 or 50/50 mix) were randomized to continue their regimen or switch to biphasic insulin lispro (50/50 mix). There was a significant improvement in $HbA_{1c}$ following the transition to premixed insulin lispro. This change in therapy did not affect quality of life; however, patients reported an improvement in convenience with biphasic insulin lispro.[144] Sharma et al. evaluated the effects of switching patients to a rapid-acting insulin regimen. Patients with poorly controlled type 2 diabetes mellitus on biphasic human insulin were switched to biphasic insulin aspart 30. There was a significant improvement in $HbA_{1c}$, fasting plasma glucose and postprandial glucose, as well as a reduction in hypoglycemic episodes following the transition to biphasic insulin aspart 30.[145] Yokoyama et al. evaluated the effects of switching patients from basal NPH insulin (administered at bedtime) to insulin glargine (administered in the morning) or continuing their existing NPH insulin therapy. Patients continued on their existing prandial insulin regimen. There was a significant reduction in $HbA_{1c}$ in patients who used insulin glargine compared to patients who continued NPH insulin. The risk of hypoglycemia did not significantly increased with the switch the morning insulin glargine.[138] Kanazawa et al. evaluated the effects of switching patients with type 1 or type 2 diabetes mellitus to insulin glargine from NPH insulin.[101] After 3 months, $HbA_{1c}$ levels improved significantly after switching to insulin glargine. The frequency of mild-to-moderate hypoglycemia was lower in the insulin glargine group.[136] Dornhorst et al. evaluated the effects of switching patients with type 2 diabetes who were on NPH insulin or insulin glargine to insulin detemir.[102] All patients continued their current oral antidiabetic medications. Glycemic control improved significantly in patients switched to insulin detemir, regardless of their previous therapy with NPH insulin or insulin glargine. The incidence of total and nocturnal hypoglycemic episodes were reduced in patients who were switch from NPH insulin ($P<0.0001$) or insulin glargine ($P<0.01$ and $P<0.05$, respectively) to insulin detemir. The incidence of major hypoglycemic events did not differ significantly from baseline. Mean body weight was also significantly reduced in patients who were switched from NPH insulin ($P<0.01$) or insulin glargine ($P<0.05$) to insulin detemir.[148]

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 9. Relative Cost of the Insulins**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| **Rapid-Acting Insulins** | | | | |
| Insulin aspart | injection | NovoLog® | $$$$$ | N/A |
| Insulin glulisine | injection | Apidra®, Apidra Solostar® | $$$$ | N/A |
| Insulin lispro | injection | Humalog® | $$$$$ | N/A |
| **Short-Acting Insulins** | | | | |
| Insulin regular, human | injection | Humulin®‡ R, Novolin®‡ R | $$$$ | N/A |
| **Intermediate-Acting Insulins** | | | | |
| NPH, human insulin isophane | injection | Humulin®‡ N, Novolin®‡ N | $$$$ | N/A |
| **Long-Acting Insulins** | | | | |
| Insulin detemir | injection | Levemir® | $$$$$ | N/A |
| Insulin glargine, human recombinant analog | injection | Lantus®, Lantus Solostar® | $$$$$ | N/A |
| **Combination Insulins (Intermediate-Acting and Rapid-Acting)** | | | | |
| Insulin aspart protamine and insulin aspart | injection | NovoLog® Mix 70/30 | $$$$$ | N/A |
| Insulin lispro protamine and insulin lispro | injection | Humalog® Mix 50/50, Humalog® Mix 75/25 | $$$$$ | N/A |
| **Combination Insulins (Intermediate-Acting and Short-Acting)** | | | | |
| NPH, human insulin isophane and insulin regular, human | injection | Humulin®‡ 70/30, Novolin®‡ 70/30 | $$$$ | N/A |

‡Product is available over-the-counter.
N/A=Not available

## X. Conclusions

The insulins have been shown to improve glycemic control in adults and children with diabetes mellitus. There are two types of insulin preparations currently available: human insulin and insulin analogs. They are categorized based on their duration of action, which includes rapid-acting, short-acting, intermediate-acting and long-acting insulins. There are no generic products available; however, some insulins are available over-the-counter.

According to current clinical guidelines regarding the management of type 1 diabetes, initiation of individualized, intensive insulin therapy at the time of diagnosis is recommended. Furthermore, overall approaches for management include the use of multiple dose injections or a subcutaneous insulin infusion, and matching of pre-prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. According to the American Diabetes Association, insulin analogs should be utilized in most patients. In addition, use of a continuous subcutaneous insulin infusion is indicated in certain clinical settings, particularly when glycemic control is difficult to achieve, during pregnancy, or when the patient does not demonstrate a willingness to comply with a multiple injection regimen. As mentioned previously, insulin regimens should be tailored to the specific clinical circumstances in individual patients, and patients should have access to the types (preparation and species) of insulin therapy they find allow them optimal well-being. In general, pre-prandial rapid-acting insulin analogs should be administered 20 to 30 minutes prior to a meal. Regular insulin might be considered, instead of rapid-acting, to obtain better control of post-prandial and premeal glucose levels in patients with gastroparesis. Some patients treated with basal, or long-acting, insulin may require twice-daily dosing to achieve greater control. Basal insulin should be provided by the use of isophane (NPH) or long-acting insulin analogs. Use of long-acting analogs should occur when nocturnal hypoglycemia is a problem with NPH, when morning hypoglycemia on NPH results in difficult daytime blood glucose control, or when rapid-acting insulin analogs are used for mealtime blood glucose control. Use of biphasic rapid-acting analog mixes (i.e., combination insulins) may be advantageous in patients prone to hypoglycemia at night. In general, no one specific insulin product among the various classifications is recommended or preferred over another. Again, insulin therapy must be individualized as the products within the different classifications play specific roles in achieving adequate glycemic control in patients with type 1 diabetes. Insulin therapy may also be appropriate in the management of type 2 diabetes; however, traditionally oral antidiabetic agents are utilized. Of note, many patients with type 2 diabetes will ultimately

require insulin therapy, alone or in combination with other agents, to maintain glucose control. Insulin is recognized as a potential option to be added to current oral antidiabetic agent regimens in patients not achieving glycemic goals. It may also be appropriate to initiate insulin therapy at the time of diagnosis in certain clinical settings, particularly in patients with a high baseline glycosylated hemoglobin ($HbA_{1c}$) (≥9.0%), or in patients presenting with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$. Furthermore, such therapy is mandatory when catabolic features are exhibited or if ketonuria is demonstrated.[18-30]

Numerous clinical trials have established the efficacy/safety of insulin therapy as monotherapy, as well as in combination with other antidiabetic agents.[31-148] For the treatment of type 1 diabetes mellitus, several studies have compared the efficacy and safety of prandial insulin regimens, while maintaining stable basal insulin regimens. The use of rapid-acting insulin analogs has resulted in a similar, or greater, reduction in $HbA_{1c}$ compared to regular insulin. The rate of hypoglycemia was found to be either similar, or lower, with the rapid-acting insulin analogs compared to regular insulin.[31-34,38,40] Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing $HbA_{1c}$, achieving similar self-monitored glucose profiles, rates of hyperglycemia, and achieving glycemic goals in type 1 diabetics.[35-37] Other trials have evaluated the efficacy and safety of various basal insulin regimens, while maintaining stable prandial insulin regimens. The use of long-acting insulin analogs has resulted in a similar, or greater, reduction in $HbA_{1c}$ compared to NPH insulin. The rate of hypoglycemia was found to be either similar, or lower, with the long-acting insulin analogs compared to NPH insulin.[56,58-68,70,73,76,77,79] Two trials directly compared insulin detemir and insulin glargine as basal therapy, while maintaining stable therapy with insulin aspart. There was a similar reduction in $HbA_{1c}$ reported in both studies and the overall rates of hypoglycemia did not differ among the treatment groups. However, nocturnal hypoglycemia was significantly lower with insulin detemir (reported in only one study).[56,57] Two studies compared insulin aspart and insulin lispro administered through a continuous subcutaneous insulin infusion. There was no difference in $HbA_{1c}$ at the end of the 16-week trials and the rates of hypoglycemia were similar among the treatment groups.[43,44]

For the treatment of type 2 diabetes mellitus, several studies have compared the efficacy and safety of insulin therapy alone, or in combination with oral antidiabetic drugs. The use of rapid-acting insulin analogs has resulted in a similar, or greater, reduction in $HbA_{1c}$ compared to regular insulin. There was no difference in hypoglycemic episodes reported among the treatment groups.[47,49,50,52,53] The majority of the studies comparing long-acting insulin analogs to NPH insulin have demonstrated similar reductions in $HbA_{1c}$.[87-89,91,95-97,99-101] However, the long-acting insulin analogs were associated with less hypoglycemia than NPH insulin.[88,89,91,95-101] Two studies directly compared insulin detemir with insulin glargine and showed no difference in $HbA_{1c}$ after 52 weeks of treatment.[82,84] A third study reported a greater reduction in $HbA_{1c}$ with insulin glargine than insulin detemir after 26 weeks of therapy (-1.28% vs -1.08%, respectively; P=0.035); however, the difference between the two treatments (0.207%) was not clinically meaningful.[83] There was no difference in the risk of overall hypoglycemia in any of the studies.[82-84] In a study comparing biphasic insulin lispro (75/25 mix) and biphasic insulin aspart (70/30 mix), there was no significant difference in $HbA_{1c}$ or overall hypoglycemia reported among the treatment groups.[48]

In summary, the insulin analogs have been shown to be at least as effective, or more effective, than human insulin. In several studies, there was a lower risk of hypoglycemia with the insulin analogs compared to human insulin. There is insufficient evidence to conclude that one rapid-acting insulin analog is safer or more efficacious than another. There is also insufficient evidence to conclude that one long-acting insulin analog is safer or more efficacious than another.

Therefore, all brand products within the class reviewed, with the exception of rapid-acting and long-acting insulin analogs, are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Rapid-acting insulin analogs offer significant clinical advantages in general use over short-acting human insulin, but are comparable to each other. Long-acting insulin analogs offer significant clinical advantages in general use over intermediate-acting human insulin, but are comparable to each other.

## XI. Recommendations

No brand insulin, with the exception of rapid-acting and long-acting insulin analogs, is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand rapid-acting insulin analog is selected as a preferred agent.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting insulin analog is selected as a preferred agent.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Meglitinides
# AHFS Class 682016
# November 14, 2014

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service (AHFS) classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The meglitinides are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-3] They are short-acting agents that decrease blood glucose concentrations by stimulating insulin secretion. Meglitinides interact with the ATP-dependent potassium channel on pancreatic beta cells.[4-5] Blockade of the potassium channel leads to depolarization of the beta cell, which opens the calcium channel. The increased calcium influx induces insulin secretion. Insulin release is glucose dependent and diminishes at low glucose concentrations. Both nateglinide and repaglinide are highly tissue selective with low affinity for heart and skeletal muscle.[1,2]

Repaglinide is also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[3]

The meglitinides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Nateglinide is available in a generic formulation. This class was last reviewed in May 2010.

**Table 1. Meglitinides Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Nateglinide | tablet | Starlix®* | nateglinide |
| Repaglinide | tablet | Prandin® | Prandin® |
| **Combination Products** | | | |
| Repaglinide and metformin | tablet | PrandiMet® | none |

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Meglitinides**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[4] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[5] (2012)** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | Initial drug therapy<br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br>Advancing to dual combination therapy<br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.<br>• Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.<br>• It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.<br>• For all medications, consideration should also be given to overall tolerability.<br><br>Advancing to triple combination therapy<br>• Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.<br>• Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.<br>• In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.<br>• Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. |

**Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations**

| **Initial Drug Monotherapy** | Metformin |
|---|---|
| Efficacy (↓$HbA_{1c}$) | High |
| Hypoglycemia | Low risk |
| Weight | Neutral/loss |
| Side Effects | Gastrointestinal/lactic acidosis |

If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)

| **Two Drug Combin-ations** | Metformin + sulfonyl-urea | Metformin + thia-zolidinedione (TZD) | Metformin + DPP-4 inhibitor | Metformin + GLP-1 receptor agonist | Metformin + insulin (usually basal) |
|---|---|---|---|---|---|
| Efficacy (↓$HbA_{1c}$) | High | High | Inter-mediate | High | Highest |
| Hypo-glycemia | Moderate risk | Low risk | Low risk | Low risk | High risk |
| Weight | Gain | Gain | Neutral | Loss | Gain |
| Major Side Effects | Hypo-glycemia | Oedema, heart failure, bone fracture | Rare | Gastro-intestinal | Hypo-glycemia |

If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)

| **Three Drug Combin-ations** | Metformin + sulfonyl-urea + | Metformin + TZD + | Metformin + DPP-4 inhibitor + | Metformin + GLP-1 receptor agonist + | Metformin + insulin therapy + |
|---|---|---|---|---|---|
| | TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonyl-urea, TZD, or insulin | Sulfonyl-urea, TZD, or insulin | TZD, DPP-4 inhibitor, or GLP-1 receptor agonist |

If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents

| **More Complex Insulin Strategies** | Insulin (multiple daily doses) |
|---|---|

| | |
|---|---|
| American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[6] (2012)** | • Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.<br>• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.<br>• It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. |
| American Association of Clinical Endocrinologists: **Medical Guidelines for** | Antihyperglycemic pharmacotherapy<br>• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[7] (2011)** | American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[8]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology** | <u>Principles underlying the algorithm</u><br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[8] (2009)** | • Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br>Stratification by current $HbA_{1c}$<br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%<br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • The following triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + GLP-1 receptor agonist + glinide.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>  ○ Metformin + DPP-4 inhibitor + glinide.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist.<br>  ○ Metformin + DPP-4 inhibitor.<br>  ○ Metformin + TZD.<br>  ○ Metformin + sulfonylurea.<br>  ○ Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>  ○ Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>  ○ Metformin + GLP-1 receptor agonist.<br>  ○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  ○ Metformin + DPP-4 inhibitor.<br>  ○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>  ○ Metformin + TZD.<br>  ○ Metformin + TZD + sulfonylurea.<br>  ○ Metformin + GLP-1 receptor agonist + TZD.<br>  ○ Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of |

| Clinical Guideline | Recommendation(s) |
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| | hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[9] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>  ○ Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>  ○ Initiate self-monitoring blood glucose levels.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>• First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>• After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>• Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>• Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>• Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[10] (2009)** | <u>DPP-4 inhibitors</u><br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br><u>TZDs</u><br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  o A body mass index ≥35 $kg/m^2$ in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI <35 $kg/m^2$, and thera$^{p}$y with insulin would have significant occupational implications or weight loss would |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | benefit other sig[n]ificant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  o A person prefers injecting insulin immediately before a meal<br>  o Hypoglycemia is a problem.<br>  o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>  o Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>  o Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>  o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>  o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>• Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[11] (2008)** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br><u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>  o The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>  o A sulfonylurea if metformin is not tolerated.<br>  o Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br><u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u><br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/$m^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  o Inadequate blood glucose control ($HbA_{1c}$ ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  o Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  o Continue with metformin and the sulfonylurea (and acarbose, |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | if used)<br>○ Review the use of the sulfonylurea if hypoglycemia occurs<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>○ Continue with metformin<br>○ Continue the sulfonylurea initially and discontinue if hypoglycemia occurs<br>• Consider combining pioglitazone with insulin therapy for:<br>○ Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>○ Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>○ Those who require assistance from a care taker or healthcare professional to administer their insulin injections<br>○ Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes<br>○ Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ is >9.0%. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>○ Immediate injection before a meal is preferred.<br>○ Hypoglycemia is a problem.<br>○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI):<br>**Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[12] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes[13] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br>Insulin<br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the meglitinides are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Meglitinides[1-3]**

| Indication | Single Entity Agents | | Combination Products |
|---|---|---|---|
| | Nateglinide | Repaglinide | Repaglinide and metformin |
| Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus | ✔ | ✔ | |
| Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone | | | ✔ |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the meglitinides are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the Meglitinides[14]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| **Single Entity Agents** | | | | | |
| Nateglinide | 73 | 97 to 99 | Liver, extensive (% not reported) | Renal (13 to 14), Feces (10) | 1.25 to 2.90 |
| Repaglinide | 56 | >98 | Liver, complete (% not reported) | Renal (8), Feces (90%) | 1 |
| **Combination Products** | | | | | |
| Repaglinide and metformin | 56/50 to 60 | >98/Negligible (% not reported) | Liver, complete (% not reported)/Liver, none (% not reported) | Renal (8), Feces (90)/Renal (90) | 1.0/6.2 |

## V. Drug Interactions

Significant drug interactions with the meglitinides are listed in Table 5.

**Table 5. Significant Drug Interactions with the Meglitinides[15]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Metformin | 1 | Iodinated contrast materials, parenteral | Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis. |
| Meglitinides | 2 | Cyclosporine | Cyclosporine may inhibit meglitinide metabolism (cytochrome P450 3A4 isoenzyme) and organic anion transporting polypeptide 1B1-mediated hepatic uptake, causing elevated plasma levels of meglitinide. Monitor blood glucose levels when starting or stopping cyclosporine and adjust the meglitinide dose as needed. |
| Meglitinides | 2 | Rifamycins | Rifamycins may increase metabolism (cytochrome P450 3A4 isoenzyme) of repaglinide during the first-pass and elimination phases, causing plasma concentrations of repaglinide to be decreased. Monitor blood glucose levels when starting or stopping rifamycin therapy and adjust meglitinide dose as needed. |
| Repaglinide | 2 | Gemfibrozil | Gemfibrozil may inhibit repaglinide metabolism (cytochrome P450 2C8 isoenzyme) causing elevated repaglinide plasma concentrations and increasing the risk of severe and protracted hypoglycemia. Avoid coadministration of repaglinide and gemfibrozil and reduce the dose of repaglinide when used together. |
| Repaglinide | 2 | Macrolide antibiotics | Certain macrolide antibiotics may inhibit the first-pass metabolism (cytochrome P450 3A4 isoenzyme) of repaglinide, causing elevated plasma levels of repaglinide and subsequently increased pharmacologic and adverse effects. |

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| | | | Monitor blood glucose levels when starting or stopping macrolide and related antibiotic therapy and adjust the repaglinide dose as needed. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

The most common adverse drug events reported with the meglitinides are listed in Table 6. The boxed warning for repaglinide/metformin is listed in Table 7.

**Table 6. Adverse Drug Events (%) Reported with the Meglitinides[1-3,14,15]**

| Adverse Events | Single Entity Agents | | Combination Products |
|---|---|---|---|
| | Nateglinide | Repaglinide | Repaglinide and metformin |
| **Cardiovascular** | | | |
| Arrhythmia | - | ≤1 | ≤1 |
| Chest pain | - | <2 | <2 |
| EEG abnormal | - | ≤1 | ≤1 |
| Hypertension | - | ≤1 | ≤1 |
| Myocardial infarction | - | ≤1 | ≤1 |
| Palpitations | - | ≤1 | ≤1 |
| **Central Nervous System** | | | |
| Dizziness | 4 | - | - |
| Headache | - | 9 to 11 | 22 |
| **Dermatologic** | | | |
| Pruritus | ✔ | - | - |
| Rash | ✔ | - | - |
| Urticaria | ✔ | - | - |
| **Endocrine/Metabolic** | | | |
| Hypoglycemia | 2 | 16 to 31 | 33 |
| **Gastrointestinal** | | | |
| Constipation | - | 2 to 3 | - |
| Diarrhea | 3.2 | 4 to 5 | 19 |
| Dyspepsia | - | 2 to 4 | - |
| Nausea | - | 3 to 5 | 15 |
| Vomiting | - | 2 to 3 | >5 |
| **Hepatic** | | | |
| Hepatic dysfunction | - | ✔ | ✔ |
| Hepatitis | ✔ | ✔ | ✔ |
| Jaundice | ✔ | ✔ | ✔ |
| **Laboratory Test Abnormalities** | | | |
| Hemolytic anemia | - | ✔ | ✔ |
| Liver enzymes increased | ✔ | ✔ | ✔ |
| Thrombocytopenia | - | ✔ | ✔ |
| Uric acid increased | ✔ | - | - |
| **Musculoskeletal** | | | |
| Arthralgia | 3 | 3 to 6 | - |
| Back pain | 4 | 5 to 6 | - |
| Paresthesia | - | 2 to 3 | - |
| **Respiratory** | | | |
| Bronchitis | 2.7 | 2 to 6 | - |
| Coughing | 2.4 | - | - |

| Adverse Events | Single Entity Agents | | Combination Products |
|---|---|---|---|
| | Nateglinide | Repaglinide | Repaglinide and metformin |
| Rhinitis | - | 3 to 7 | - |
| Sinusitis | - | 3 to 6 | - |
| Upper respiratory infection | 10 | 10 to 16 | 11 |
| **Other** | | | |
| Accidental trauma | 2.9 | - | - |
| Allergy | - | 1 to 2 | - |
| Alopecia | - | ✔ | ✔ |
| Anaphylactic reaction | - | ✔ | ✔ |
| Blurred vision | - | ✔ | ✔ |
| Flu symptoms | 4 | - | - |
| Pancreatitis | - | ✔ | ✔ |
| Stevens-Johnson Syndrome | - | ✔ | ✔ |
| Tooth disorder | - | 2 | - |
| Urinary tract infection | - | 2 to 3 | - |
| Weight gain | ✔ | - | - |

✔ Percent not specified.
-Event not reported.

**Table 7. Boxed Warning for Repaglinide/Metformin[3]**

| WARNING |
|---|
| Lactic acidosis: Lactic acidosis is a rare but serious complication that can occur because of metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic function impairment, renal function impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, discontinue repaglinide/metformin and hospitalize the patient immediately. |

## VII. Dosing and Administration

The usual dosing regimens for the meglitinides are listed in Table 8.

**Table 8. Usual Dosing Regimens for the Meglitinides[1-3]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Nateglinide | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: initial, 60 to 120 mg TID before meals; maintenance, 120 mg TID before meals | Safety and efficacy in children have not been established. | Tablet:<br>60 mg<br>120 mg |
| Repaglinide | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: initial, 0.5 to 2 mg with meals; maintenance, 0.5 to 4 mg with meals; maximum, 16 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>0.5 mg<br>1 mg<br>2 mg |
| **Combination Products** | | | |
| Repaglinide and metformin | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a meglitinide and metformin or who have inadequate | Safety and efficacy in children have not been established. | Tablet:<br>1-500 mg<br>2-500 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | glycemic control on a meglitinide alone or metformin alone:<br>Tablet: initial, 1-500 mg BID to TID with meals, unless the patient is already taking higher coadministered doses of repaglinide and metformin; maximum, 4-1,000 mg/day | | |

BID=twice daily, TID=three times daily

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the meglitinides are summarized in Table 9.

**Table 9. Comparative Clinical Trials with the Meglitinides**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Type 2 Diabetes – Monotherapy** | | | | |
| Rosenstock et al.[16] (2004)<br><br>Nateglinide 60 mg TID before each meal (titrated to a maximum of 360 mg daily)<br><br>vs<br><br>repaglinide 0.5 mg TID before each meal (titrated to a maximum of 16 mg daily) | MC, OL, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m$^2$, $HbA_{1c}$ 7.0 to 12.0%, and drug naïve | N=150<br><br>16 weeks | Primary:<br>Final $HbA_{1c}$ and changes in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Changes in FPG from baseline | Primary:<br>Mean baseline $HbA_{1c}$ values were similar in both groups (8.9%). The changes in $HbA_{1c}$ for repaglinide from baseline were -1.57 vs -1.04% for nateglinide (P=0.002). Final $HbA_{1c}$ values were lower in the repaglinide group vs the nateglinide group (7.3 vs 7.9%, respectively).<br><br>At the end of the study, 54% of the repaglinide-treated patients had $HbA_{1c}$ values ≤7.0% vs 42% of nateglinide-treated patients (P=0.18).<br><br>Secondary:<br>The final FPG was 154.0±40.2 mg/dL for repaglinide and 188.0±62.2 mg/dL for nateglinide. The mean change from baseline in FPG was greater with repaglinide compared to nateglinide (-57 vs -18 mg/dL; P<0.001).<br><br>There were no major hypoglycemic episodes (requiring the assistance of another person) in either treatment group.<br><br>Mean weight gains from baseline to the study end point were 1.8 kg for repaglinide and 0.7 kg for nateglinide (incremental mean imputation method calculation P=0.04 and P=0.034 by last observed carried forward method calculation).<br><br>The most common adverse events (3 to 10% of patients in both treatment groups) were upper respiratory tract infection, sinusitis, constipation, arthralgia, headache, and vomiting. There were no notable differences in the pattern of adverse events for the treatment groups. |
| Li et al.[17] (2007)<br><br>Nateglinide 90 mg TID before each | DB, DD, MC, RCT<br><br>Chinese patients 35 to 65 years of age with type 2 | N=223<br><br>12 weeks | Primary:<br>FPG, $HbA_{1c}$, TG, TC, BMI, HOMA-IR, β-cell function indexes, plasma | Primary:<br>Compared to baseline, FPG; 30-, 60-, and 120-minute PPG; and $HbA_{1c}$ all decreased significantly with both repaglinide and nateglinide treatment (P<0.05). Effects on FPG and PPG of the two agents were not significantly different (P>0.05). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| meal<br><br>vs<br><br>repaglinide 1 mg TID before each meal | diabetes, on a stable diet and exercise for 4 weeks, with fasting blood glucose ≥7.8 mmol/L and/or 2-hour PPG ≥11.1 mmol/L at least twice in 2 weeks, without a history of antidiabetic agents other than metformin (on stable dosage for 4 weeks) | | insulin, C-peptide, PPG using the incremental AUC ($AUC_{0\text{-}120\ min}$) after a standard 800-kcal meal (55% carbohydrate, 25% fat and 20% protein)<br><br>Secondary:<br>Not reported | The $HbA_{1c}$ levels at week 12 of the repaglinide group and the nateglinide group were not significantly different (6.27 vs 6.59%, respectively; P>0.05). However, an $HbA_{1c}$ reduction at week 12 from baseline in the repaglinide group was significantly greater than an $HbA_{1c}$ reduction in the nateglinide group (-1.21 vs -0.68%, respectively; P=0.0039).<br><br>AUC of glucose significantly decreased in both repaglinide and nateglinide groups at week 12 to a similar extent (20.36±4.67 vs 20.54±4.83 mmol/L/h, respectively; P<0.0001 vs baseline; P>0.05 between the groups).<br><br>AUC of insulin and C-peptide in both groups were increased at week 12 to a similar extent (P<0.05 vs baseline; P>0.05 between two groups).<br><br>HOMA-IR in both groups were decreased significantly, and effects of repaglinide and nateglinide on insulin sensitivity were not different (2.44 vs 2.48, at week 12 respectively; P<0.05 vs baseline; P>0.05 between the groups).<br><br>β-cell function indexes were increased in both groups, but the values were not significantly different between two groups after 12 weeks of treatment (P<0.05 vs baseline; P>0.05 between the groups).<br><br>After the 12 weeks of treatment with repaglinide, TG level significantly decreased from baseline (no values reported; P<0.05). In both groups, TC level was decreased from baseline at week 12 (no values reported; P<0.05), and BMI was reduced slightly (P>0.05). Effects of both agents on TG, TC and BMI were not different (no values reported; P>0.05).<br><br>Adverse events between the groups were reported to be similar (P>0.05). However, the rate of adverse reaction was reported to be 4.5% (hypoglycemic event, thrombocytopenia, elevation of liver enzymes) in the repaglinide group and 0.87% (thrombocytopenia) in the nateglinide group.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Not reported |
| Hollander et al.[18] (2003)<br><br>Nateglinide 120 mg TID before each meal<br><br>vs<br><br>glyburide 5 mg to 10 mg QD<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 32 to 75 years of age with type 2 diabetes ≥3 months prior to entry into the trial on diet modification alone for ≥4 weeks before initial visit, mean $HbA_{1c}$ 6.8 to 11.0%, and a BMI 20 to 35 $kg/m^2$ | N=152<br><br>8 weeks | Primary:<br>Change from week 0 to week eight during liquid meal challenges in FPG, fasting insulin, fasting C-peptide, and fasting proinsulin<br><br>Secondary:<br>Not reported | Primary:<br>At week eight, FPG was reduced more with glyburide compared to nateglinide (-1.9 mmol/L; P<0.001).<br><br>Nateglinide treatment did not have significant changes from baseline with fasting levels of C-peptide, insulin, or proinsulin.<br><br>Glyburide treatment increased fasting C-peptide vs placebo and nateglinide (P<0.001), fasting insulin vs placebo (P<0.001) and nateglinide (P<0.05), and proinsulin vs placebo (P<0.001) and nateglinide (P<0.025).<br><br>Reduction of mealtime glucose excursions from nateglinide was approximately twice that from glyburide (-4.94±0.74 vs -2.71±0.71 mmol/hr/L; P<0.03).<br><br>The insulin secretion reflected by the C-peptide AUCs was approximately twice that in the glyburide group than in the nateglinide group (1.83±0.24 vs 0.95±0.23 nmol/hr/L, respectively; P=0.063 vs nateglinide).<br><br>Secondary:<br>Not reported |
| Wolffenbuttel et al.[19] (1999)<br><br>Repaglinide 0.5 to 4 mg TID before each meal<br><br>vs<br><br>glyburide 1.75 to 10.5 mg daily | DB, MC, PG, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes who were being treated with oral blood glucose-lowering agents and/or diet, BMI 21 to 35 $kg/m^2$, and an $HbA_{1c}$ >6.5% when treated with diet only and <12% | N=424<br><br>12 months | Primary:<br>Change in $HbA_{1c}$ and FPG from baseline to the final visit<br><br>Secondary:<br>Change in fasting insulin and lipid levels and four-point blood glucose levels (fasting, before lunch, before | Primary:<br>Change in $HbA_{1c}$ levels was not different between groups when compared to baseline. $HbA_{1c}$ levels increased by 0.58% (95% CI, 0.41 to 0.76) in the repaglinide group and by 0.45% (95% CI, 0.22 to 0.69) in the glyburide group.<br><br>In a subset of patients who were treated previously with diet only, $HbA_{1c}$ decreased significantly more during glyburide treatment (–2.4%) vs repaglinide (–1%; P<0.05). The changes in $HbA_{1c}$ in patients who were already being treated with oral agents were similar, 0.6% in the repaglinide group and 0.7% in the glyburide group.<br><br>Changes in fasting plasma glucose from baseline showed a similar trend as the $HbA_{1c}$. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | when treated with diet plus oral blood glucose-lowering agents | | supper, and at bedtime) from baseline to the final visit | Secondary:<br>Mean fasting insulin levels decreased in the repaglinide group (–3 pmol/L) and increased in the glyburide group (+1 pmol/L). There was no treatment difference.<br><br>Changes from baseline in four-point glucose levels were small for both treatment groups.<br><br>Lipid levels (TC, HDL, and TG) did not change during the study. |
| Derosa et al.[20] (2003)<br><br>Repaglinide 1 to 2.5 mg daily<br><br>vs<br><br>glimepiride 1 to 3 mg daily | DB, PC, RCT<br><br>Patients with type 2 diabetes for ≥6 months, drug naïve, and $HbA_{1c}$ >7.0% with diet and exercise | N=124<br><br>12 months | Primary:<br>Changes from baseline in $HbA_{1c}$, FPG, PPG, fasting plasma insulin, lipoprotein(a), plasminogen activator inhibitor-1, homocysteine, body weight, BMI, postprandial insulin, BP, TC, LDL-C, HDL-C, TG, apolipoprotein A-1, apolipoprotein B, and fibrinogen<br><br>Secondary:<br>Not reported | Primary:<br>Changes in $HbA_{1c}$ and FPG from baseline were significant for both treatments (P<0.01).<br><br>Changes in PPG were significant for repaglinide vs baseline (P<0.01) and compared to glimepiride (P<0.05). Changes in PPG from baseline for the glimepiride group was significant (P<0.05).<br><br>Change in fasting plasma insulin from baseline was significant for repaglinide (P<0.05).<br><br>Changes in lipoprotein(a) from baseline were significant for repaglinide (P<0.05) and glimepiride (P<0.01).<br><br>Changes in plasminogen activator inhibitor-1 from baseline were significant for both treatment groups (P<0.05).<br><br>Changes in homocysteine were significant from baseline for repaglinide (P<0.05) and glimepiride (P<0.01). Changes in homocysteine were significant for glimepiride vs repaglinide (P<0.05).<br><br>There were no significant changes during the study from baseline at six or 12 months in the following parameters for either treatment group: body weight, BMI, postprandial insulin, BP, TC, LDL-C, HDL-C, TG, apolipoprotein A-1, apolipoprotein B, and fibrinogen.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Cesur et al.[21] (2007)<br><br>Repaglinide up to 4 mg QD<br><br>vs<br><br>glimepiride up to 8 mg QD<br><br>vs<br><br>insulin glargine up to 36 U QD | MC, OL, OS, PRO<br><br>Patient 33 to 67 years of age with type 2 diabetes, $HbA_{1c}$ 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month | N=65<br><br>Duration not specified | Primary:<br>FBG, PPG, $HbA_{1c}$, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramandan fasting<br><br>Secondary:<br>Not reported | Primary:<br>In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan.<br><br>In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods).<br><br>There was no significant change in $HbA_{1c}$ levels between the nonfasting and fasting groups.<br><br>There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan (P<0.01 for both).<br><br>BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and post-Ramadan in nonfasting group).<br><br>TC, LDL-C, and TG did not change throughout the study period but HDL-C levels significantly increased at post-Ramadan in the fasting group (P<0.01). In nonfasting group, LDL-C and TG levels significantly increased at post-Ramadan (P<0.05 for both).<br><br>At least one hypoglycemia episode was reported in 12.2% of patients in the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Taki et al.[22] (2005)<br><br>Nateglinide | OS<br><br>Patients with type 2 diabetes, drug naïve, with FPG ≤150 mg/dL and had started to take nateglinide alone | N=547<br><br>12 weeks | Primary:<br>$HbA_{1c}$, PPG, FPG, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>In the nateglinide group, a reduction in $HbA_{1c}$ was 0.82%, PPG was 59.4 to 158.0 mg/dL, and FPG was 11.7 to 122.4 mg/dL.<br><br>Hypoglycemia was the most prevalent adverse event (2.1%). A total of nine of 11 episodes required no therapeutic intervention. Severe hypoglycemia was recognized in one case of diabetes complicated by serious renal dysfunction, for which nateglinide has been contraindicated in Japan. No patient experienced symptoms of nocturnal or prolonged hypoglycemia.<br><br>Secondary:<br>Not reported |
| Taki et al.[23] (2006)<br><br>Nateglinide | OS<br><br>Japanese patients with type 2 diabetes | N=1,014<br><br>15 months | Primary:<br>PPG, FPG, $HbA_{1c}$, BMI<br><br>Secondary:<br>Not reported | Primary:<br>In patients receiving nateglinide, there were reductions in PPG of -9.3 mg/dL (from 155.1±40.0 to 145.0±35.1 mg/dL) and $HbA_{1c}$ of 0.68% (from 7.51±1.36 to 6.83±1.09%).<br><br>In patients previously treated with sulfonylurea, a decrease in $HbA_{1c}$ was not observed.<br><br>No change in BMI was noted after 15 months of nateglinide treatment.<br><br>Secondary:<br>Not reported |
| Schwarz et al.[24] (2008)<br><br>Nateglinide 120 mg TID before meals<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients 65 to 90 years of age with type 2 diabetes for ≥4 weeks, oral antidiabetic agents, with FPG ≤240 mg/dL, BMI 22 to 40 mg/m$^2$, $HbA_{1c}$ 7.0 to 9.5%, without | N=54<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, PPG, proportion of patients achieved a target $HbA_{1c}$ <7.0 or ≤6.5%, adverse events | Primary:<br>Plasma $HbA_{1c}$ decreased from 7.6±0.1 to 6.9±0.1% in patients receiving nateglinide (mean change, -0.7±0.1%; P<0.001) compared to a reduction of 7.7± 0.2 to 7.5±0.1% in patients receiving placebo (change, -0.2±0.2%; P=0.206). A significant difference between the two groups in $HbA_{1c}$ change was reported (-0.5%; 95% CI, -1.0 to -0.2; P=0.004).<br><br>Secondary:<br>After 12 weeks of treatment, FPG decreased significantly from 164±6 to 141±7 mg/dL in patients receiving nateglinide (change, -23±7 mg/dL; P=0.003) compared to a reduction of 153±8 to 159±7 mg/dL in patients receiving placebo (change, 2±5 mg/dL; P=0.728). A significant difference |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | history of type 1 diabetes or secondary diabetes, significant symptomatic complications of diabetes, severe cardiac dysfunction, significant cardiovascular events within 6 months prior to randomization, and severe liver disease | | | between the two groups in FPG change was reported (-25 mg/dL; 95% CI, -40 to -3; P=0.022).<br><br>Two-hour PPG decreased from 184±11 to 153±8 mg/dL in patients receiving nateglinide (change, -29±11 mg/dL; P=0.019) compared to a reduction of 192±14 to 188±15 mg/dL in patients receiving placebo (change, -7±17 mg/dL; P=0.687). A difference between two groups in Two-hour PPG change was significant (-36 mg/dL; 95% CI, -74 to -8; P=0.018).<br><br>Sixty percent of patients in the nateglinide group achieved a target $HbA_{1c}$ of <7.0% compared to 21% of patients in the placebo group (P=0.004).<br><br>Significantly higher number of patients receiving nateglinide achieved a target $HbA_{1c}$ ≤6.5% compared to placebo-treated patients (8/30 vs 1/24, respectively; P=0.028).<br><br>Similar adverse-event profiles were reported between the two groups (15 patients in each group reported one or more adverse events). No serious adverse events, hypoglycemic events or deaths were reported. |
| Chisalita et al.[25] (2009)<br><br>Repaglinide 4 mg TID before meals for 10 weeks<br><br>vs<br><br>insulin aspart 13 to 46 units/day (4 to 20 units at breakfast, 5 to 15 units at lunch and 4 to 15 units at dinner) for 10 weeks | XO<br><br>Patients ≥60 years of age with type 2 diabetes | N=5<br><br>20 weeks | Primary:<br>$HbA_{1c}$, blood glucose, C-peptide, free human insulin, free total (human and analogue) insulin, proinsulin, islet amyloid polypeptide, growth hormone binding protein, and plasma lipoprotein concentrations were measured | Primary:<br>The $HbA_{1c}$ was 6.1% at the end of repaglinide therapy and 5.9% at the end of insulin aspart therapy (P value not significant).<br><br>C-peptide concentrations were significantly higher during repaglinide treatment compared to insulin aspart treatment (AUC 2,453 vs 1,153; P=0.02).<br><br>Free human insulin levels were significantly higher on repaglinide than on insulin aspart therapy (AUC: 215 vs 128; P<0.05).<br><br>Proinsulin levels were higher when measured during repaglinide treatment than during treatment with insulin aspart.<br><br>Islet amyloid polypeptide levels tended to be higher during repaglinide compared to insulin aspart treatment (P value not significant). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | Secondary:<br>Not reported | Fasting plasma insulin like growth factor-I concentration was 220 ng/mL during treatment with insulin aspart and 226 ng/mL during treatment with repaglinide (P value not significant).<br><br>Compared to fasting levels, the insulin like growth factor binding protein-1 levels were lower during repaglinide (P<0.05), but not during insulin aspart treatment (P value not significant).<br><br>Repaglinide treatment increased plasma growth hormone binding protein concentration compared with insulin aspart (1,094 vs 942 pmol/L; P=0.02).<br><br>Repaglinide treatment resulted in higher postprandial plasma TC, TG and apolipoprotein B concentrations compared with insulin aspart. There was no significant difference in LDL-C or HDL-C<br><br>Secondary:<br>Not reported |
| Lund et al.[26] (2008)<br><br>Repaglinide 2 mg TID for 4 months<br><br>vs<br><br>metformin 1,000 mg BID for 4 months | DD, XO<br><br>Non-obese (BMI ≤27 kg/m$^2$), insulin-naïve patients with type 2 diabetes mellitus | N=96<br><br>8 months with 1 month washout | Primary:<br>Cardiovascular disease biomarkers and metabolic regulation<br><br>Secondary:<br>Not reported | Primary:<br>Levels of tumor necrosis factor-alpha, plasminogen activator inhibitor-1 antigen, tissue-type plasminogen activator antigen, von Willebrand factor, soluble intercellular adhesion molecule-1 and soluble E-selectin were significantly lower during metformin treatment compared with repaglinide treatments.<br><br>Amadori albumin and heart rate were higher during metformin compared with repaglinide.<br><br>Both treatment groups experienced similar levels of interleukin-6, fibrinogen, soluble vascular cell adhesion molecule-1, asymmetric dimethylarginine and advanced glycation end products as well as glycemic levels and 24 hour BP.<br><br>Secondary:<br>Not reported |
| Lund et al.[27] (2008) | DD, XO | N=192 | Primary:<br>Postprandial | Primary:<br>Both treatment groups equally changed fasting levels and total AUC for |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Repaglinide 2 mg TID for 4 months<br><br>vs<br><br>metformin 1,000 mg BID for 4 months | Non-obese (BMI ≤27 kg/m$^2$), insulin-naïve patients with type 2 diabetes mellitus | 8 months with 1 month washout | metabolism with blood sampling 0 to six hours postprandially<br><br>Secondary:<br>Not reported | plasma glucose, TG and FFA.<br><br>The metformin treatment group obtained lower fasting levels and AUC of TC, LDL-C, and non-HDL-C and serum insulin compared with repaglinide. After adjusting for fasting levels, AUC differences still remained significant.<br><br>Secondary:<br>Not reported |
| Bolen et al.[28] (2007)<br><br>Meglitinides<br><br>vs<br><br>biguanides<br><br>vs<br><br>TZDs<br><br>vs<br><br>α-glucosidase inhibitors<br><br>vs<br><br>second-generation sulfonylureas | MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)<br><br>Patients with type 2 diabetes | N=136 (articles on intermediate outcomes)<br><br>N=167 (articles on adverse events)<br><br>N=68 (articles on micro-vascular outcomes and mortality)<br><br>Duration varied | Primary:<br>Intermediate outcomes: $HbA_{1c}$, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes<br><br>Secondary:<br>Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events | Primary:<br>Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in $HbA_{1c}$ level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.<br><br>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.<br><br>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.<br><br>Most agents except metformin increased body weight by 1 to 5 kg.<br><br>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05).<br><br>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive |

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| | | | | heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).<br><br>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.<br><br>Secondary:<br>According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).<br><br>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.<br><br>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.<br><br>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents. |
| Monami et al.[29] (2008)<br><br>Metformin<br><br>vs<br><br>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists | MA<br><br>Patients with type 2 diabetes mellitus | N=7,890 (27 RCT)<br><br>Variable duration | Primary:<br>Reduction in $HbA_{1c}$ at 16 to 36 months<br><br>Secondary:<br>Not reported | Primary:<br>Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in $HbA_{1c}$ by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.<br><br>In direct comparisons, sulfonylureas led to a greater reduction in $HbA_{1c}$ (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.<br><br>Secondary:<br>Not reported |
| Saenz et al.[30] | MA (29 RCTs) | N=5,259 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| (2005)<br><br>Metformin monotherapy<br><br>vs<br><br>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin | Adult patients with type 2 diabetes | ≥3 months | Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality<br><br>Secondary:<br>Changes in $HbA_{1c}$, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro- | Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).<br><br>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02).<br><br>Secondary:<br>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for $HbA_{1c}$ when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | albuminuria, glomerular filtration rate, renal plasma flow | |
| Gangji et al.[31] (2007)<br><br>Glyburide<br><br>vs<br><br>sulfonylureas, meglitinides, insulin | MA (21 trials)<br><br>Patients with type 2 diabetes | N=not reported<br><br>Duration varied | Primary:<br>Hypoglycemia, glycemic control, cardiovascular events, body weight, death<br><br>Secondary:<br>Not reported | Primary:<br>Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52; 95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49).<br><br>Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues.<br><br>Secondary:<br>Not reported |
| Richter et al.[32] (2007)<br><br>Rosiglitazone monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial)<br><br>or<br><br>rosiglitazone combination therapy vs a similar | MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | 18 trials<br><br>N=3,888 randomized to rosiglitazone treatment (total N not reported)<br><br>24 weeks to 4 years (median 26 weeks) | Primary:<br>Patient-oriented outcomes including mortality, morbidity, adverse effects<br><br>Secondary:<br>Health-related quality of life, metabolic control ($HbA_{1c}$) | Primary:<br>No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference).<br><br>The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).<br><br>The percentage of overall adverse events was comparable between the |

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| combination with another compound (8 trials)<br><br>Some studies had more than 1 treatment arm. | | | | intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in body mass index up to 1.5 $kg/m^2$. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).<br><br>Secondary:<br>No study investigated health-related quality of life.<br><br>Active glucose-lowering compounds like metformin, glibenclamide* or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to rosiglitazone treatment. |
| Richter et al.[33] (2006)<br><br>Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a | MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | 22 trials<br><br>N=6,200 randomized to pioglitazone treatment (total N not reported)<br><br>24 weeks to 34.5 months | Primary:<br>Patient-oriented outcomes including mortality, morbidity, adverse effects<br><br>Secondary:<br>Health-related quality of life, $HbA_{1c}$ | Primary:<br>Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).<br><br>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The |

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| sulfonylurea (8 trials)<br><br>or<br><br>pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)<br><br>Some studies had more than 1 treatment arm. | | | | individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).<br><br>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in body mass index up to 1.5 kg/m$^2$. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.<br><br>Secondary:<br>No study investigated health-related quality of life.<br><br>Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to pioglitazone treatment (P values not reported). |
| **Type 2 Diabetes – Combination Therapy** | | | | |
| Raskin et al.[34] (2003)<br><br>Nateglinide 120 mg TID before meals and metformin 1,000 mg BID<br><br>vs | MC, OL, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes for ≥3 months, BMI 24 to 42 kg/m$^2$, $HbA_{1c}$ 7.0 to 12.0% on previous monotherapy with a | N=192<br><br>16 weeks | Primary:<br>Final $HbA_{1c}$ values and changes in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Changes in FPG and assessment of glucose area under | Primary:<br>Mean $HbA_{1c}$ changes from baseline were significantly greater in the repaglinide group compared to the nateglinide group (-1.28 vs -0.67%; P<0.001).<br><br>The final $HbA_{1c}$ at 16 weeks was 7.1±1.1% for the repaglinide group and 7.5±1.4% for the nateglinide group.<br><br>The percent of patients who achieved final $HbA_{1c}$ values ≤7.0% was 59% for the repaglinide group and 47% for the nateglinide group (P value not |

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| repaglinide 1 to 4 mg TID before meals and metformin 1,000 mg BID | sulfonylurea, metformin, or low dose glyburide plus metformin | | the time concentration curves from 0 to 240 minutes ($AUC_{0\text{-}240\ min}$), insulin $AUC_{0\text{-}240\ min}$, and glucagon $AUC_{0\text{-}240\ min}$ after a liquid test meal at baseline and at study end point | reported).<br><br>Secondary:<br>FPG values were significantly different between the two treatment groups with one week of therapy. Mean changes in FPG values from baseline were significantly greater for the repaglinide group (-39 vs -21 mg/dL for nateglinide group; P=0.002). The final FPG at 16 weeks was 150.0±45.1 mg/dL for the repaglinide group and 170±52 mg/dL for the nateglinide group. At the end of the 16 week maintenance study, 48% of the repaglinide group had reductions of FPG values >40 mg/dL and 26% of the nateglinide group had a response of this magnitude.<br><br>Mean end point reductions in PPG levels from baseline were not significantly different between the groups (glucose $AUC_{0\text{-}240\ min}$). The treatments were also similar for changes in insulin $AUC_{0\text{-}240\ min}$ and glucagon $AUC_{0\text{-}240\ min}$ during the study (P values not reported).<br><br>There were no patients in either group who experienced major hypoglycemic episodes (requiring the assistance of another person).<br><br>The most frequent adverse event in both groups was upper respiratory infection (12 vs 21%). Adverse events that occurred from 3 to 8% included nausea, viral infection, accidental injury, sinusitis, diarrhea, and headache. The repaglinide group had 5% incidence of chest pain and arthralgia, as compared to 1% for each in the nateglinide groups. Mean changes from baseline in weight were small for both groups, 0.6 kg gain for repaglinide compared to 0.5 kg loss with nateglinide. |
| Horton et al.[35] (2000)<br><br>Nateglinide 120 mg TID before each meal and metformin 500 mg TID immediately after the start of each meal | DB, PC, PRO, RCT<br><br>Patients ≥30 years of age with type 2 diabetes for ≥3 months with a BMI 20 to 35 kg/m$^2$, and all patients needed to have been treated with diet alone with | N=701<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$, FPG, glucose AUC after Sustacal challenge from baseline<br><br>Secondary:<br>Not reported | Primary:<br>Adjusted mean change from baseline in $HbA_{1c}$, FPG, and glucose AUC after Sustacal challenge were significantly reduced from baseline (P≤0.0001) in patients receiving active treatment.<br><br>$HbA_{1c}$, FPG, and glucose AUC were all significantly reduced compared to placebo (P≤0.001), except from glucose AUC with metformin monotherapy.<br><br>The decrease in $HbA_{1c}$ was greater for metformin compared to nateglinide, |

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| vs<br><br>nateglinide 120 mg TID before each meal<br><br>vs<br><br>metformin 500 mg TID immediately after the start of each meal<br><br>vs<br><br>placebo | an $HbA_{1c}$ 6.8 to 11.0% and FPG level ≤15 mmol/L | | | the between group difference was small (0.3% difference; P≤0.01).<br><br>The decrease in FPG was greater with the metformin group compared to the nateglinide group, the between group difference was 0.9 mmol/L (P<0.001).<br><br>The combination of nateglinide plus metformin was additive ($HbA_{1c}$, -1.4% and FPG, -2.4 mmol/L; P≤0.01 vs either monotherapy).<br><br>After a Sustacal challenge, there was a greater reduction in mealtime glucose with nateglinide compared to metformin or placebo ($AUC_{0\text{-}130\ min}$, -2.1, -1.1, and 0.6 mmol/hr/L, respectively; P≤0.0001). A greater reduction was seen with nateglinide plus metformin ($AUC_{0\text{-}130\ min}$, -2.5 mmol/hr/L; P≤0.0001 vs metformin and placebo).<br><br>Secondary:<br>Not reported |
| Marre et al.[36] (2002)<br><br>Nateglinide 60 to 120 mg TID before meals and metformin 1,000 mg BID<br><br>vs<br><br>metformin 1,000 mg BID and placebo | DB, MC, PG, RCT<br><br>Patients ≥30 years of age with type 2 diabetes for ≥6 months with $HbA_{1c}$ 6.8 to 11.0%, BMI 20 to 35 kg/m$^2$, and were treated with metformin for a minimum of 3 months and stabilized at a dose of ≥1,500 mg/day for ≥4 weeks prior to study entry | N=467<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change in FPG, body weight, and lipid profile (TC, fasting TGs, LDL-C, HDL-C) | Primary:<br>Mean $HbA_{1c}$ was reduced significantly from baseline when compared to the placebo group for the nateglinide 60 mg group (-0.36%; 95% CI, -0.59 to -0.13; P=0.003) and for the nateglinide 120 mg group (-0.51%; 95% CI, -0.82 to -0.36; P<0.001) at end point.<br><br>Dose-dependent reduction in $HbA_{1c}$ was seen with nateglinide irrespective of baseline parameters, with larger mean reductions seen with nateglinide 120 mg. There was little or no change in $HbA_{1c}$ at end point in the placebo group.<br><br>Secondary:<br>There were modest changes from baseline in FBG in the nateglinide groups and an increase was seen in the placebo group, the difference compared to baseline was significant in both the nateglinide 60 and 120 mg groups (P=0.044 and P=0.003, respectively).<br><br>There were no notable changes in body weight at end point in the patients that received placebo (0.1 kg) or nateglinide 60 mg (0.4 kg). There was a significant increase (P<0.001) in mean weight of 0.9 kg in the nateglinide |

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| | | | | 120 mg group as compared to baseline.<br><br>Fasting TGs were significantly reduced in the nateglinide 120 mg group as compared to the placebo group at end point (P=0.042). The mean changes in TC, LDL-C, and HDL-C remained almost unchanged throughout the study. |
| Gerich et al.[37] (2003)<br><br>Nateglinide 120 mg TID before meals and metformin 500 to 2,000 mg daily<br><br>vs<br><br>glyburide 1.25 to 10 mg daily and metformin 500 to 2,000 mg daily | DB, MC, RCT (PRESERVE-β Study)<br><br>Men and women aged 18 to 77 years with type 2 diabetes, drug naïve, $HbA_{1c}$ 7.0 to 11.0%, FPG ≤15 mmol/L, BMI of 22 to 45 kg/m$^2$ and inadequately controlled on diet and exercise | N=428<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline (average of weeks -2 and 0) to week 104<br><br>Secondary:<br>Change from baseline to week 104 in FPG, and body weight | Primary:<br>Both treatments maintained similar reductions in $HbA_{1c}$. The mean change in $HbA_{1c}$ from baseline to week 104 in the nateglinide plus metformin group (–1.2 ±0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (–1.5 ±0.1%). The changes in $HbA_{1c}$ were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups.<br><br>Secondary:<br>Mean change in FPG was –1.6±0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and –2.4±0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).<br><br>Body weight decreased in the nateglinide plus metformin group (–0.4 kg±0.4 kg) and increased in the glyburide plus metformin group (0.8 kg±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115). |
| Schwarz et al.[38] (2008)<br><br>Nateglinide 120 mg TID before meals and metformin 2,000 mg QD<br><br>vs | AC, DB, MC, RCT (PRESERVE-β Study – subgroup analysis)<br><br>Men and women ≥65 years old with type 2 diabetes, drug naïve, $HbA_{1c}$ 7.0 to 11.0%, FPG ≤15 mmol/L, BMI | N=69<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change from baseline to week 104 in FPG, two-hour PPG using the incremental AUC ($AUC_{0\text{-}120\ min}$) of | Primary:<br>Similar reductions in $HbA_{1c}$ were seen with both treatments. The average change in $HbA_{1c}$ from baseline to week 104 in the nateglinide plus metformin group (–1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (–1.2±0.1%). The changes in $HbA_{1c}$ were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups.<br><br>Secondary:<br>Mean change in FPG was –26±6 mg/dL in patients receiving nateglinide |

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| glyburide 10 mg QD and metformin 2,000 mg QD | 22 to 45 kg/m$^2$ | | glucose during oral glucose tolerance tests, the proportion of patients achieving a target $HbA_{1c}$ <7.0 or ≤6.5%, adverse events | plus metformin (P<0.001 vs baseline) and –36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups).<br><br>A non-significant reduction in two-hour PPG from baseline was reported in both the nateglinide plus metformin and glyburide plus metformin groups (–15±7 mg/dL; P=0.071 and –8±8 mg/dL; P=0.385, respectively).<br><br>The proportion of patients who achieved a target $HbA_{1c}$ <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736).<br><br>Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target $HbA_{1c}$ ≤6.5% (40 and 60%, respectively; P=0.206).<br><br>Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs eight mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023). |
| Fonseca et al.[39] (2003)<br><br>Nateglinide 120 mg before each meal and rosiglitazone 8 mg QD<br><br>vs<br><br>rosiglitazone 8 mg QD and placebo | DB, MC, PC, RCT<br><br>Patients ≥21 years of age with type 2 diabetes for ≥6 months previously and treated with rosiglitazone 8 mg/day, diet, and exercise for ≥3 months, had a BMI 22 to 40 kg/m$^2$, FPG 6.1 to 13.3 mmol/L, and $HbA_{1c}$ 7.0 to 11.0% | N=402<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, two-hour postprandial insulin, TC, LDL-C, HDL-C, TG, body weight, four-hour AUC for glucose, insulin during meal challenges | Primary:<br>$HbA_{1c}$ did not change significantly from baseline in the placebo group, but did change significantly in the nateglinide group. The change from baseline to end point was -0.8±0.1% (P<0.0001 vs baseline or placebo).<br><br>Secondary:<br>Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide group (P<0.001). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo.<br><br>Two-hour postprandial insulin in the nateglinide group decreased from 14.0 to 11.4 mmol/L (P<0.0001). The group receiving placebo had an increase in two-hour postprandial insulin from 14.4 to 14.8 mmol/L (P<0.0001 vs nateglinide).<br><br>Total and incremental glucose $AUCs_{(0\text{-}4\ hours)}$ were significantly reduced in |

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| | | | | the nateglinide group (-8.6±0.8 and -6.2±0.5 mmol/L/hr, respectively; P<0.0001 vs baseline or placebo for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC.<br><br>Total and incremental insulin $AUCs_{(0\text{-}4\ hour)}$ were increased in the nateglinide group (425 and 395 pmol/L/hr, respectively; P<0.0001 vs baseline or placebo plus for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC.<br><br>There were no significant changes in TC, LDL-C, or TG in either group. There was a small, but significant increase from baseline in HDL-C observed in patients receiving nateglinide (P<0.025) and in patients receiving placebo (P<0.005).<br><br>Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide (3.1±0.3 kg) was significantly greater compared to patients receiving placebo (1.1±0.3 kg; P<0.0001).<br><br>Meal challenges were performed at week 0 and at end point. The glucose and insulin profiles were similar in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients receiving placebo. |
| Moses et al.[40] (1999)<br><br>Repaglinide 0.5 to 4 mg TID before each meal and metformin 1,000 to 3,000 mg daily<br><br>vs<br><br>repaglinide 0.5 to | DB, MC, PG, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes treated with metformin alone (1 to 3 g/day) for >6 months and had not achieved optimal glycemic control ($HbA_{1c}$ >7.0%) and BMI ≥21 kg/m$^2$ | N=83<br><br>3 months | Primary:<br>Change in baseline $HbA_{1c}$ and FPG<br><br>Secondary:<br>Change in fasting insulin, C-peptide levels, fasting TG, TC, HDL-C, LDL-C, free fatty acids, body weight | Primary:<br>Patients in the metformin plus repaglinide group had a significant decrease in $HbA_{1c}$ from 8.3 to 6.9% (P=0.0016) and FPG from 10.2 to 8.0 mmol/L (P=0.0003) compared to baseline. There were no significant changes in $HbA_{1c}$ or FPG for patients receiving metformin alone and repaglinide alone. The $HbA_{1c}$ and FPG changes from baseline for metformin plus repaglinide vs metformin alone and metformin plus repaglinide vs repaglinide were significant (P<0.05 for all).<br><br>Secondary:<br>Fasting insulin and C-peptide levels increased significantly from baseline in both groups receiving repaglinide (P<0.05 for both). |

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| 4 mg TID before each meal<br><br>vs<br><br>metformin 1,000 to 3,000 mg daily | | | | Lipid levels (TC, HDL-C, LDL-C, TG, FFA) did not change significantly from baseline in the metformin plus repaglinide group. No significant differences were found between the metformin plus repaglinide group and the monotherapy groups.<br><br>In both groups receiving repaglinide there was an increase in body weight which was significant compared to baseline (P<0.05 for both). |
| Raskin et al.[41] (2004)<br><br>Repaglinide 0.5 to 4 mg TID before meals and rosiglitazone 2 to 4 mg BID<br><br>vs<br><br>repaglinide 0.5 to 4 mg TID before meals<br><br>vs<br><br>rosiglitazone 2 to 4 mg BID | MC, OL, PG, RCT<br><br>Patients ≥18 years old with type 2 diabetes for ≥12 months with an $HbA_{1c}$ >7.0 to ≤12.0% during previous monotherapy with sulfonylurea or metformin for ≥3 months with a BMI ≤45 kg/m$^2$ | N=252<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG | Primary:<br>Mean change in $HbA_{1c}$ from baseline with repaglinide was -0.17% and -0.56% with rosiglitazone. The mean change in $HbA_{1c}$ from baseline with combination therapy was -1.43 (P≤0.001 vs either monotherapy). The reduction in $HbA_{1c}$ from baseline was greater with combination therapy compared to the sum of the responses for monotherapy (P<0.01).<br><br>Secondary:<br>Mean FPG change from baseline with repaglinide was -3 mmol/L and -3.7 mmol/L with rosiglitazone. Mean FPG change from baseline with combination therapy was -5.2 mmol/L (P≤0.001 vs either monotherapy). |
| Ozbek et al.[42] (2006)<br><br>Repaglinide 4.5 mg QD<br><br>vs<br><br>placebo<br><br>All patients were | RCT<br><br>Patients with type 2 diabetes who had been initially treated with oral antidiabetic agents without a satisfactory response ($HbA_{1c}$ <7.0%), | N=50<br><br>3 months | Primary:<br>Exogenous insulin requirements, $HbA_{1c}$, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>A significant reduction in daily total exogenous insulin requirements was seen in the repaglinide group. The daily total insulin requirements were 57.4±14.8 and 28.8±13.8 units before and after the three month study period, respectively (P<0.01).<br><br>Serum $HbA_{1c}$ levels were 7.3±0.3 and 6.4±0.3% before and after the three month period in the repaglinide group (P<0.01).<br><br>None of the patients experienced symptomatic hypoglycemia episode. |

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| also receiving insulin. | hospitalized in a single centre for glycemic control with intensive insulin therapy involving multiple daily subcutaneous injections | | | Secondary:<br>Not reported |
| Civera et al.[43] (2008)<br><br>Repaglinide 2mg TID before meals, metformin 850mg BID, and NPH insulin before dinner<br><br>vs<br><br>metformin 850mg BID and NPH insulin before dinner<br><br>vs<br><br>NPH insulin BID | OL, PG<br><br>Patients with poorly controlled type 2 diabetes despite being on two or more oral antidiabetic drugs | N=37<br><br>24 weeks | Primary:<br>$HbA_{1c}$, hypoglycemia, body weight<br><br>Secondary:<br>Not reported | Primary:<br>The $HbA_{1c}$ was lower in the repaglinide triple therapy group (7.2%) compared to the metformin plus NPH insulin group (8.8%; P=0.02) and the NPH insulin group (8.4%; P=0.02).<br><br>The absolute reduction in $HbA_{1c}$ was -2.4% in the repaglinide triple therapy group compared to -0.7% (P=0.01) in the metformin plus NPH insulin group and -1.4% in the insulin NPH group.<br><br>Lower PPG values were seen with the repaglinide triple therapy group compared to the other two treatment groups (P<0.01).<br><br>Significant differences in weight gain and hypoglycemia were not seen.<br><br>Secondary:<br>Not reported |
| Wang et al (abstract).[44]<br><br>Repaglinide 1 mg TID, titrated up to 4 mg TID<br><br>vs | AC, OL, PG, RCT<br><br>Patients 18 to 75 years of age with type 2 diabetes, $HbA_{1c}$ >8.5%, BMI ≤35 kg/m$^2$, and who were naïve to oral antidiabetic agents, | N=432<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, two-hour PPG, seven-point plasma glucose, safety | Primary:<br>Mean $HbA_{1c}$ reduction was 4.51±1.64% with combination therapy and 4.05±1.59% with repaglinide. Estimated mean treatment difference for combination therapy vs repaglinide was -0.30% (95% CI, -0.49 to -0.11; P< 0.01).<br><br>Secondary:<br>Combination therapy demonstrated significant improvements compared to repaglinide in FPG, seven-point plasma glucose, and lunchtime and |

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|---|---|---|---|---|
| repaglinide 1 mg TID plus metformin 500 mg TID, titrated up to 4 mg TID and 500 mg TID | | | | dinnertime two-hour PPG (P<0.05 for all).<br><br>Hypoglycemia rates were 2.04 events/patient-year with combination therapy compared to 1.35 events/patient-year with repaglinide (P=0.058). Adverse events were comparable between the two treatments. |
| Derosa et al.[45] (2009)<br><br>Nateglinide 60 mg TID and metformin 1,500 to 3,000 mg daily<br><br>vs<br><br>glyburide 7.5 to 12.5 mg daily and metformin 1,500 to 3,000 mg daily | DB, MC, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes mellitus, $HbA_{1c}$ >7.0%), BMI 25 to 28 kg/m$^2$, and hypertensive (SBP/DBP, >130/≥85 mmHg) | N=248<br><br>12 months | Primary:<br>Changes in BMI, FPG and PPG, $HbA_{1c}$, fasting and postprandial plasma insulin, HOMA index, and lipid profile [TC, LDL-C, HDL-C, TG, apolipoprotein A-I, and apolipoprotein B, SBP, and DBP<br><br>Secondary:<br>Not reported | Primary:<br>BMI did not show any significant change during the study.<br><br>A significant reduction in $HbA_{1c}$ was shown after nine months (P<0.05) and 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in $HbA_{1c}$ was seen with glyburide after 12 months (P<0.05) compared to baseline. The $HbA_{1c}$ at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05).<br><br>After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline.<br><br>Significant changes in PPG were found at nine months (P<0.05) in the nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline.<br><br>Fasting plasma insulin and postprandial insulin did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline.<br><br>HOMA index decrease was obtained only at 12 months (P<0.05) compared to the baseline value in both groups,<br><br>No significant change was observed in TC, LDL-C, HDL-C, TG, apolipoprotein A-I, apolipoprotein B, SBP, DBP and heart rate in either group after three, six, nine and 12 months.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Swinnen et al.[46] (2010)<br><br>Continuation of secretagogues (sulfonylureas or meglitinides)<br><br>vs<br><br>discontinuation of secretagogues (sulfonylureas or meglitinides)<br><br>All patients received existing metformin regimens and initiated insulin therapy. | PRO<br><br>Patients 40 to 75 years of age with type 2 diabetes, $HbA_{1c}$ 7.0 to 10.5% receiving oral glucose-lowering drugs | N=865<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Hypoglycemia, body weight, insulin dose | Primary:<br>In patients continuing secretagogue treatment, $HbA_{1c}$ decreased to 7.0±0.8% at week 12 compared to 7.4±0.9% in patients discontinuing their secretagogues. Endpoint $HbA_{1c}$ level was 7.2±0.9% in both treatment groups. The difference in mean $HbA_{1c}$ reduction during the trial was not significant (-1.59±1.08% for patients continuing secretagogues and -1.30±1.14% for patients discontinuing secretagogues; P=0.382).<br><br>Secondary:<br>Compared to patients who discontinued secretagogues, patients who continued secretagogues experienced significantly more hypoglycemia (40.0 vs 24.5%; P<0.001) and gained significantly more weight (1.44±3.04 vs 0.43±3.00 kg; P<0.001).<br><br>End of trial insulin doses, were significantly lower in patients who continued secretagogues compared to patients who discontinued secretagogues (P<0.001). |
| Black et al.[47] (2007)<br><br>Meglitinide<br><br>vs<br><br>meglitinide and metformin<br><br>vs<br><br>meglitinide and insulin<br><br>vs | MA (15 trials)<br><br>Patients with type 2 diabetes | N=3,781<br><br>Duration varied | Primary:<br>Mortality and morbidity<br><br>Secondary:<br>Change in $HbA_{1c}$, weight or BMI, hypoglycemia, adverse effects, quality of life | Primary:<br>No trials reported the effect of meglitinides on mortality and morbidity.<br><br>Secondary:<br>In the 11 trials comparing meglitinides to placebo, both repaglinide and nateglinide resulted in reductions in $HbA_{1c}$ (0.1 to 2.1% and 0.2 to 0.6%, respectively). In two trials comparing repaglinide to nateglinide, reduction in $HbA_{1c}$ was similar. When compared to metformin, both repaglinide and nateglinide showed similar or slightly smaller reduction in $HbA_{1c}$ compared to metformin. The combination therapy of metformin plus a meglitinide showed a clinically significant reduction in $HbA_{1c}$ compared to metformin.<br><br>Weight gain was generally greater in patients receiving meglitinides compared to patients receiving metformin. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| metformin<br><br>vs<br><br>placebo | | | | Evidence from the meglitinide trials with metformin suggests that both repaglinide and nateglinide had fewer gastrointestinal adverse events including diarrhea. There was no evidence of serious adverse events associated with meglitinides.<br><br>There were more reports of hypoglycemia episodes in patients receiving meglitinides compared to patients receiving placebo. In the two head-to-head trials of repaglinide and nateglinide, fewer patients receiving nateglinide reported hypoglycemia symptoms (2 vs 7%). When compared to metformin, patients receiving meglitinides reported more hypoglycemia episodes.<br><br>There were two trials that assessed quality of life in patients receiving repaglinide vs placebo and in patients receiving repaglinide plus insulin vs metformin plus insulin. There were no substantial changes in quality of life using a variety of validated diseases specific and nonspecific tools. Treatment satisfaction using the World Health Organization DTSQ improved significantly in patients receiving repaglinide compared to patients receiving placebo. |

*Synonym for glyburide.
†Product not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, DBP=diastolic blood pressure, DTSQ=Diabetes Treatment Satisfaction Questionnaire, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=Glucagon-like peptide-1, $HbA_{1c}$=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, OR=odds ratio, PPG=postprandial plasma glucose, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 10. Relative Cost of the Meglitinides**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| **Single Entity Agents** | | | | |
| Nateglinide | tablet | Starlix®* | $$$$ | $$$ |
| Repaglinide | tablet | Prandin® | $$$$$ | N/A |
| **Combination Products** | | | | |
| Repaglinide and metformin | tablet | PrandiMet® | $$$$-$$$$$ | N/A |

*Generic is available in at least one dosage form or strength.
N/A=Not available

## X. Conclusions

The meglitinides are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-3] Nateglinide is the only agent that is currently available in a generic formulation.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin ($HbA_{1c}$) will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The meglitinides are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note that meglitinides are associated

with a limited $HbA_{1c}$-lowering ability, weight gain, and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. In addition, guidelines recognize the potential use of meglitinides when postprandial hyperglycemia is present. Among all current clinical guidelines, preference of one meglitinide over another is not stated.[4-13]

The meglitinides have been evaluated in a variety of clinical trials. Three studies have directly compared nateglinide and repaglinide, either as monotherapy or in combination with metformin. In all three studies, the mean change in $HbA_{1c}$ from baseline was significantly greater with repaglinide compared to nateglinide.[16,17,34] The meglitinides have also been compared to sulfonylureas in monotherapy studies. Glyburide was found to be more effective than nateglinide in one study, whereas glyburide and repaglinide were found to be equally efficacious in another study.[18,19] The combination of nateglinide and metformin was shown to be as effective, or more effective, than the combination of glyburide and metformin in two studies.[37,45] Several studies evaluated the efficacy of meglitinides in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[35,36,39-42]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the meglitinides or any other antidiabetic drug.

There is insufficient evidence to support that one brand meglitinides is safer or more efficacious than another within its given indication. Since the meglitinides are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand meglitinide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Sulfonylureas
# AHFS Class 682020
# November 14, 2010

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The sulfonylureas are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-10] They stimulate the release of insulin from functioning pancreatic beta cells.[1-10] There may also be additional extrapancreatic effects; however, the mechanism by which these agents lower blood glucose during long-term administration has not been clearly established. The sulfonylureas block ATP-dependent potassium channels in pancreatic beta cells. This leads to depolarization of the beta cell, followed by an influx of calcium and stimulation of insulin secretion.[11,12]

The sulfonylureas may be further classified as first generation or second generation agents. The first generation sulfonylureas include chlorpropamide, tolazamide and tolbutamide. The second generation sulfonylureas include glimepiride, glipizide and glyburide. The second generation agents have structural characteristics that allow them to be given in much lower doses than the first generation agents. The sulfonylureas primarily differ in their pharmacokinetic parameters; however, they appear to have similar glucose-lowering effects when administered in equipotent doses.[11,12]

Glipizide and glyburide are also available in combination with metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[4,7]

The sulfonylureas that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the sulfonylureas are available in a generic formulation, including the fixed-dose combination products. This class was last reviewed in May 2010.

**Table 1. Sulfonylureas Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Chlorpropamide | tablet | N/A | chlorpropamide |
| Glimepiride | tablet | Amaryl®* | glimepiride |
| Glipizide | extended-release tablet, tablet | Glucotrol®*, Glucotrol XL®* | glipizide, glipizide extended-release |
| Glyburide | tablet | DiaBeta®* | glyburide |
| Glyburide, micronized | tablet | Glynase®* | glyburide, micronized |
| Tolazamide | tablet | N/A | tolazamide |
| Tolbutamide | tablet | N/A | tolbutamide |
| **Combination Products** | | | |
| Glipizide and metformin* | tablet | N/A | glipizide and metformin |
| Glyburide, micronized and metformin | tablet | Glucovance®* | glyburide, micronized and metformin |

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List
N/A=Not available

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Sulfonylureas**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[13] (2012)** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes<br>• An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association | Key points |

| Clinical Guideline | Recommendation(s) |
|---|---|
| (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[14] (2012)** | • Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible.<br>• Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy.<br><br><u>Initial drug therapy</u><br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br><u>Advancing to dual combination therapy</u><br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. |

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- Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
- It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.
- For all medications, consideration should also be given to overall tolerability.

Advancing to triple combination therapy

- Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
- Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
- In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
- Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

**Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations**

| **Initial Drug Monotherapy** | Metformin |
|---|---|
| Efficacy (↓$HbA_{1c}$) | High |
| Hypoglycemia | Low risk |
| Weight | Neutral/loss |
| Side Effects | Gastrointestinal/lactic acidosis |
| If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference) | |

| **Two Drug Combin-ations** | Metformin + sulfonyl-urea | Metformin + thia-zolidinedione (TZD) | Metformin + DPP-4 inhibitor | Metformin + GLP-1 receptor agonist | Metformin + insulin (usually basal) |
|---|---|---|---|---|---|
| Efficacy (↓$HbA_{1c}$) | High | High | Inter-mediate | High | Highest |
| Hypo-glycemia | Moderate risk | Low risk | Low risk | Low risk | High risk |
| Weight | Gain | Gain | Neutral | Loss | Gain |
| Major Side Effects | Hypo-glycemia | Oedema, heart failure, bone fracture | Rare | Gastro-intestinal | Hypo-glycemia |
| If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference) | | | | | |
| **Three Drug Combin-ations** | Metformin + sulfonyl-urea + | Metformin + TZD + | Metformin + DPP-4 inhibitor + | Metformin + GLP-1 receptor agonist + | Metformin + insulin therapy + |
| | TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonyl-urea, TZD, or insulin | Sulfonyl-urea, TZD, or insulin | TZD, DPP-4 inhibitor, or GLP-1 receptor agonist |

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| | If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents<br>**More Complex Insulin Strategies**: Insulin (multiple daily doses) |
| American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[15] (2012)** | • Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.<br>• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.<br>• It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. |
| American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[16] (2011)** | Antihyperglycemic pharmacotherapy<br>• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[17]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. |

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| | • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[17] (2009)** | <u>Principles underlying the algorithm</u><br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action.<br>• Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br><u>Stratification by current $HbA_{1c}$</u><br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br><u>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%</u><br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors |

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| | are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration.<br>• The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + GLP-1 receptor agonist + glinide.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + DPP-4 inhibitor + glinide.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + TZD.<br>  o Metformin + sulfonylurea.<br>  o Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial |

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| | weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>  o Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>  o Metformin + TZD.<br>  o Metformin + TZD + sulfonylurea.<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However |

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| | the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[18] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>  ○ Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>  ○ Initiate self-monitoring blood glucose levels.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>• First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>• After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• Recognize that patients currently treated with monotherapy or |

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| | combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>• Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>• Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed.<br>• Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly |

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| | offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[19] (2009)** | <u>DPP-4 inhibitors</u><br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br><u>TZDs</u><br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled. |

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| | • A TZD may be preferable to a DPP-4 inhibitor if:<br>  ○ The person has marked insulin insensitivity.<br>  ○ A DPP-4 inhibitor is contraindicated.<br>  ○ The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br><u>GLP-1 mimetics</u><br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>  ○ A body mass index ≥35 kg/m$^2$ in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI <35 kg/m$^2$, and thera$^p$y with insulin would have significant occupational implications or weight loss would benefit other sig$^n$ificant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>  ○ The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>  ○ The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>  ○ The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>  ○ The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>  ○ A person prefers injecting insulin immediately before a meal<br>  ○ Hypoglycemia is a problem.<br>  ○ Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>  ○ Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>  ○ Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>  ○ Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>  ○ Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>• Monitor a person on a basal insulin regimen (NPH insulin or a long- |

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|---|---|
| | acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[20] (2008)** | Metformin<br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.<br><br>Insulin secretagogues<br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br>Rapid-acting insulin secretagogues<br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br>Acarbose<br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br>TZDs<br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>  o The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>  o A sulfonylurea if metformin is not tolerated.<br>  o Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br>Gliptins: GLP-1 enhancers<br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br>Exenatide: GLP-1 mimetics<br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/m$^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | nature arising from high body weight.<br>  ○ Inadequate blood glucose control ($HbA_{1c}$ ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  ○ Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u><br>• May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  ○ Continue with metformin and the sulfonylurea (and acarbose, if used)<br>  ○ Review the use of the sulfonylurea if hypoglycemia occurs<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>  ○ Continue with metformin<br>  ○ Continue the sulfonylurea initially and discontinue if hypoglycemia occurs<br>• Consider combining pioglitazone with insulin therapy for:<br>  ○ Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>  ○ Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>  ○ Those who require assistance from a care taker or healthcare professional to administer their insulin injections<br>  ○ Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes<br>  ○ Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ is >9.0%. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>  ○ Immediate injection before a meal is preferred.<br>  ○ Hypoglycemia is a problem.<br>  ○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[21] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits.<br>• Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |
| International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes[22] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br>Insulin<br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the sulfonylureas are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Sulfonylureas[1-10]**

| Generic Name | Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus | Adjunct to Diet to Lower the Blood Glucose in Patients with Non-insulin-dependent Diabetes Mellitus (Type II) Whose Hyperglycemia Cannot be Controlled by Diet Alone |
|---|---|---|
| **Single Entity Agents** | | |
| Chlorpropamide | ✔ | |
| Glimepiride | ✔ | |
| Glipizide | ✔ | |
| Glyburide | ✔ | |
| Glyburide, micronized | ✔ | |
| Tolazamide | ✔ | |
| Tolbutamide | | ✔ |
| **Combination Products** | | |
| Glipizide and metformin | ✔ | |
| Glyburide, micronized and metformin | ✔ | |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the sulfonylureas are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the Sulfonylureas[23]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| **Single Entity Agents** | | | | | |
| Chlorpropamide | Not reported | 60 to 90 | Liver (% not reported) | Renal (80 to 90) | 25 to 48 |
| Glimepiride | 100 | >99 | Liver (% not reported) | Renal (60), Feces (40) | 9 |
| Glipizide | 100 | 97 to 99 | Liver (% not reported) | Renal (63 to 89), Feces (11) | 2 to 5 |
| Glyburide | Not reported | 99 | Liver (% not reported) | Renal (50), Bile (50) | 5 to 10 |
| Glyburide, micronized | Not reported | 99 | Liver (% not reported) | Renal (80 to 90) | 5 to 10 |
| Tolazamide | Not reported | Not reported | Liver (% not reported) | Renal (85), Feces (7) | 7 |
| Tolbutamide | Not reported | 80 to 99 | Liver (% not reported) | Renal (75 to 80) | 4.5 to 6.5 |
| **Combination Products** | | | | | |
| Glipizide and metformin | 100/50 to-60 | 98/Negligible | Liver | Renal (10) Bile (11)/Renal (90) | 2 to 4/6 |
| Glyburide, micronized and metformin | Not reported/50 to 60 | 99/Negligible | Liver | Renal (80 to 90)/Renal (90) | 5 to 10/6 |

## V. Drug Interactions

Significant drug interactions with the sulfonylureas are listed in Table 5.

**Table 5. Significant Drug Interactions with the Sulfonylureas[24]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Metformin | 1 | Iodinated contrast materials, parenteral | Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis. Glipizide/metformin or glyburide/metformin should not be restarted until renal function returns to normal. |
| Sulfonylureas (glimepiride, glyburide, glyburide/metformin) | 1 | Quinolones | The hypoglycemic effect of glimepiride and glyburide may be increased by quinolones, especially in elderly patients with renal compromise. The mechanism of this interaction is unknown. |
| Sulfonylureas (chlorpropamide, tolbutamide) | 2 | Anticoagulants (dicumarol) | Dicumarol can inhibit the metabolism of certain sulfonylureas and cause an increased hypoglycemic response. |
| Sulfonylureas (glimepiride, tolbutamide) | 2 | Azole antifungals | Azole antifungals may inhibit the cytochrome P450 2C9 isoenzyme-mediated metabolism of certain sulfonylureas, increasing the hypoglycemic effects. |
| Sulfonylureas (glyburide) | 2 | Bosentan | Bosentan may increase the metabolism (cytochrome P450 2C9 and 3A4 isoenzyme-mediated) of glyburide. Other mechanisms may also be involved. Plasma levels of bosentan and glyburide may be decreased. Increased risk of elevated liver enzymes, resulting in serious liver injury may occur. |
| Sulfonylureas | 2 | Diazoxide | Diazoxide may decrease endogenous insulin release and cause increases in glucose and free fatty acids, producing a decrease in glycemic control in patients stabilized on a sulfonylurea. |
| Sulfonylureas | 2 | Monoamine oxidase inhibitors (MAOIs) | MAOIs may enhance the hypoglycemic action of sulfonylureas through an unknown mechanism. |
| Sulfonylureas (chlorpropamide, glimepiride, glyburide, tolbutamide) | 2 | Rifamycins | Rifamycins may decrease the half-life and increase the clearance of certain sulfonylureas through increased metabolism. |
| Sulfonylureas (chlorpropamide, glipizide, glyburide, tolbutamide) | 2 | Sulfonamides | Sulfonamides may impair the cytochrome P450 2C9 isoenzyme-mediated metabolism of certain sulfonylureas and enhance the hypoglycemic effects of sulfonylureas. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

The most common adverse drug events reported with the sulfonylureas are listed in Table 6. The boxed warning for glipizide/metformin and glyburide/metformin is listed in Table 7. The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This association has led to a warning and is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. However it is important to note that only tolbutamide was included in this study.[1-10]

**Table 6. Adverse Drug Events (%) Reported with the Sulfonylureas[1-10]**

| Adverse Events | Single Entity Agents | | | | | | | Combination Products | |
|---|---|---|---|---|---|---|---|---|---|
| | Chlorpro-pamide | Glimep-iride | Glipizide | Glyburide | Glyburide, micronized | Tolaz-amide | Tolbut-amide | Glipizide and Metformin | Glyburide, Micronized and Metformin |
| **Cardiovascular** | | | | | | | | | |
| Chest discomfort | - | - | - | - | - | - | - | ✔ | ✔ |
| Flushing | - | - | - | - | - | - | - | ✔ | ✔ |
| Hypertension | - | - | - | - | - | - | - | 3 to 4 | - |
| Palpitations | - | - | - | - | - | - | - | ✔ | ✔ |
| Syncope | - | - | ✔ | - | - | - | - | ✔ | - |
| **Central Nervous System** | | | | | | | | | |
| Anxiety | - | - | ✔ | - | - | - | - | ✔ | - |
| Depression | - | - | ✔ | - | - | - | - | ✔ | - |
| Dizziness | ✔ | 2 | ✔ | ✔ | ✔ | ✔ | - | 2 to 5 | ✔ |
| Drowsiness | - | - | ✔ | - | - | - | - | ✔ | - |
| Fatigue | - | - | - | - | - | ✔ | - | - | - |
| Headache | ✔ | 2 | ✔ | ✔ | ✔ | ✔ | ✔ | 6 to 13 | 6 |
| Insomnia | - | - | ✔ | - | - | - | - | ✔ | - |
| Nervousness | - | - | ✔ | - | - | - | - | ✔ | - |
| Paresthesia | - | - | ✔ | ✔ | ✔ | - | - | ✔ | ✔ |
| Tremor | - | - | ✔ | - | - | - | - | ✔ | - |
| Vertigo | - | - | - | - | - | ✔ | - | - | - |
| Weakness | - | 2 | - | - | - | ✔ | - | 9 | 9 |
| **Dermatological** | | | | | | | | | |
| Allergic skin reactions | - | ✔ | ✔ | ✔ | ✔ | - | - | ✔ | ✔ |
| Angioedema | - | - | - | ✔ | ✔ | - | - | - | ✔ |
| Eczema | - | - | ✔ | - | - | - | - | ✔ | - |
| Erythema | ✔ | ✔ | ✔ | ✔ | ✔ | - | ✔ | ✔ | ✔ |
| Exfoliative dermatitis | ✔ | - | - | - | - | - | - | - | - |
| Morbilliform or | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |

| Adverse Events | Single Entity Agents | | | | | | | Combination Products | |
|---|---|---|---|---|---|---|---|---|---|
| | Chlorpro-pamide | Glimep-iride | Glipizide | Glyburide | Glyburide, micronized | Tolaz-amide | Tolbut-amide | Glipizide and Metformin | Glyburide, Micronized and Metformin |
| maculopapular eruptions | | | | | | | | | |
| Photosensitivity | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Porphyria cutanea tarda | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | - | ✔ | ✔ |
| Pruritus | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Purpura | - | - | - | ✔ | ✔ | - | - | - | ✔ |
| Rash | - | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Sweating | - | - | ✔ | - | - | - | - | ✔ | ✔ |
| Urticaria | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Vasculitis | - | ✔ | - | ✔ | ✔ | - | - | ✔ | ✔ |
| **Endocrine and Metabolic** | | | | | | | | | |
| Edema | - | ✔ | ✔ | - | - | - | - | ✔ | - |
| Hypoglycemia | ✔ | 1 to 2 | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Hyponatremia | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Lactic acidosis | - | - | - | - | - | - | - | ✔ | ✔ |
| Syndrome of inappropriate antidiuretic hormone | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| **Gastrointestinal** | | | | | | | | | |
| Abdominal/gastrointestinal pain | - | ✔ | - | - | - | - | - | 6 | 6 |
| Anorexia | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | - | ✔ | - |
| Constipation | - | ✔ | ✔ | ✔ | ✔ | ✔ | - | ✔ | ✔ |
| Diarrhea | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | - | 2 to 53 | 10 to 53 |
| Dyspepsia | - | - | - | - | - | - | - | ✔ | ✔ |
| Epigastric fullness | - | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Flatulence | - | - | ✔ | - | - | - | - | 12 | 12 |
| Gastralgia | - | - | ✔ | - | - | - | - | ✔ | - |
| Heartburn | - | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Hunger | ✔ | - | - | - | - | - | - | - | - |
| Indigestion | - | - | - | - | - | - | - | 7 | 7 |
| Nausea | ✔ | 1 | ✔ | ✔ | ✔ | ✔ | ✔ | 1 to 26 | 7 to 26 |
| Proctocolitis | ✔ | - | - | - | - | - | - | - | - |
| Taste alteration | - | - | - | - | - | - | ✔ | ✔ | ✔ |
| Vomiting | ✔ | ✔ | ✔ | - | - | ✔ | - | 1 to 26 | 7 to 26 |
| **Genitourinary** | | | | | | | | | |
| Diuresis | - | ✔ | ✔ | ✔ | ✔ | ✔ | - | ✔ | - |

| Adverse Events | Single Entity Agents | | | | | | | Combination Products | |
|---|---|---|---|---|---|---|---|---|---|
| | Chlorpro-pamide | Glimep-iride | Glipizide | Glyburide | Glyburide, micronized | Tolaz-amide | Tolbut-amide | Glipizide and Metformin | Glyburide, Micronized and Metformin |
| Dysuria | - | - | - | - | - | - | - | ✔ | - |
| Urinary tract infection | - | - | - | - | - | - | - | 1 | - |
| **Hematologic** | | | | | | | | | |
| Agranulocytosis | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | - |
| Aplastic anemia | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | - |
| Blood dyscrasias | - | - | ✔ | - | - | - | - | ✔ | - |
| Eosinophilia | ✔ | - | - | - | - | - | - | - | - |
| Hemolytic anemia | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Leukopenia | ✔ | ✔ | ✔ | ✔ | ✔ | - | ✔ | ✔ | - |
| Megaloblastic anemia | - | - | - | - | - | - | - | ✔ | ✔ |
| Pancytopenia | ✔ | ✔ | ✔ | ✔ | ✔ | - | - | ✔ | - |
| Thrombocytopenia | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | - |
| **Hepatic** | | | | | | | | | |
| Cholestatic jaundice | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Elevated liver enzyme levels | - | ✔ | - | - | - | - | - | - | - |
| Hepatic porphyria | ✔ | ✔ | ✔ | - | - | ✔ | ✔ | ✔ | - |
| Hepatitis | - | ✔ | - | ✔ | ✔ | - | - | - | ✔ |
| Liver function abnormalities | - | ✔ | - | ✔ | ✔ | - | - | - | ✔ |
| Transaminases increased | - | - | - | ✔ | ✔ | - | - | - | ✔ |
| **Musculoskeletal** | | | | | | | | | |
| Arthralgia | - | - | ✔ | ✔ | ✔ | - | - | ✔ | - |
| Leg cramps | - | - | ✔ | - | - | - | - | ✔ | - |
| Musculoskeletal pain | - | - | - | - | - | - | - | 8 | - |
| Myalgia | - | - | ✔ | ✔ | ✔ | - | - | ✔ | ✔ |
| **Respiratory** | | | | | | | | | |
| Pneumonitis | - | - | - | - | - | - | - | ✔ | ✔ |
| Rhinitis | - | - | ✔ | - | - | - | - | ✔ | - |
| Upper respiratory tract infection | - | - | - | - | - | - | - | ✔ | ✔ |
| **Other** | | | | | | | | | |
| Blurred vision | - | ✔ | ✔ | ✔ | ✔ | - | - | ✔ | ✔ |
| Changes in accommodation | - | ✔ | - | ✔ | ✔ | - | - | ✔ | ✔ |

| Adverse Events | Single Entity Agents | | | | | | | Combination Products | |
|---|---|---|---|---|---|---|---|---|---|
| | Chlorpro-pamide | Glimep-iride | Glipizide | Glyburide | Glyburide, micronized | Tolaz-amide | Tolbut-amide | Glipizide and Metformin | Glyburide, Micronized and Metformin |
| Chills | - | - | - | - | - | - | - | ✔ | ✔ |
| Decreased Vitamin $B_{12}$ levels | - | - | - | - | - | - | - | ✔ | ✔ |
| Disulfiram-like reaction | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Flu-like symptoms | - | - | - | - | - | - | - | ✔ | ✔ |
| Hypersensitivity reaction | - | - | - | ✔ | ✔ | - | ✔ | ✔ | ✔ |
| Nail disorder | - | - | - | - | - | - | - | ✔ | ✔ |
| Pain | - | - | ✔ | - | - | - | - | ✔ | - |

✔ Percent not specified.
-Event not reported.

**Table 7. Boxed Warning for Glipizide and metformin and Glyburide, micronized and metformin[24]**

| WARNING |
| --- |
| Lactic acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur because of metformin accumulation during treatment with glipizide/metformin; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (more than 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of more than 5 µg/mL are generally found.<br><br>The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases per 1,000 patient-years, with approximately 0.015 fatal cases per 1,000 patient-years). In more than 20,000 patient-years of exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal function impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure (CHF) requiring pharmacologic management, in particular those with unstable or acute CHF who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal function impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and the use of the minimum effective dose of metformin. In particular, accompany the treatment of elderly patients with careful monitoring of renal function. Do not initiate glipizide/metformin treatment in patients 80 years of age and older unless measurement of creatinine clearance demonstrates that renal function is not reduced, because these patients are more susceptible to developing lactic acidosis. In addition, promptly withhold glipizide/metformin in the presence of any condition associated with dehydration, hypoxemia, or sepsis. Because hepatic function impairment may significantly limit the ability to clear lactate, generally avoid glipizide/metformin in patients with clinical or laboratory evidence of hepatic disease. Caution patients against excessive alcohol intake, acute or chronic, when taking glipizide/metformin, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, temporarily discontinue glipizide/metformin prior to any intravascular radiocontrast study and for any surgical procedure.<br><br>The onset of lactic acidosis is often subtle and accompanied only by nonspecific symptoms, such as increasing somnolence, malaise, myalgia, nonspecific abdominal distress, and respiratory distress. There may be associated hypotension, hypothermia, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's health care provider must be aware of the possible importance of such symptoms. Instruct the patient to notify their health care provider immediately if symptoms occur. Withdraw glipizide/metformin until the situation is clarified. Serum electrolytes, ketones, blood glucose, and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of glipizide/metformin, gastrointestinal symptoms, which are common during initiation of therapy with metformin, are unlikely to be drug-related. Later occurrence of gastrointestinal symptoms could be caused by lactic acidosis or other serious disease.<br><br>Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking glipizide/metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.<br><br>Suspect lactic acidosis in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (e.g., ketonemia, ketonuria).<br><br>Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking glipizide/metformin, discontinue the drug immediately and institute general supportive measures promptly. Because metformin is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. |

## VII. Dosing and Administration

The usual dosing regimens for the sulfonylureas are listed in Table 8.

**Table 8. Usual Dosing Regimens for the Sulfonylureas[1-10]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Chlorpropamide | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: initial, 100 to 125 mg QD; maintenance, 100 to 500 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>100 mg<br>250 mg |
| Glimepiride | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: initial, 1 or 2 mg QD; maximum, 8 mg/day | Not recommended in pediatric patients. | Tablet:<br>1 mg<br>2 mg<br>4 mg |
| Glipizide | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Extended-release tablet: initial, 5 mg QD; maintenance, 5 to 10 mg QD; maximum, 20 mg/day<br><br>Tablet: initial, 2.5 or 5 mg QD; maximum, 40 mg/day | Safety and efficacy in children have not been established. | Extended-release tablet:<br>2.5 mg<br>5 mg<br>10 mg<br><br>Tablet:<br>5 mg<br>10 mg |
| Glyburide | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: initial, 1.25 to 5 mg QD; maintenance, 1.25 to 20 mg/day; maximum, 20 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>1.25 mg<br>2.5 mg<br>5 mg |
| Glyburide, micronized | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: initial, 0.75 to 3 mg QD; maintenance, 0.75 to 12 mg QD; maximum, 12 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>1.5 mg<br>3 mg<br>6 mg |
| Tolazamide | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: initial, 100 to 250 mg QD; maintenance, 100 to 1,000 mg QD; maximum, 1,000 mg/day | Safety and efficacy in children have not been established. | Tablet:<br>250 mg<br>500 mg |
| Tolbutamide | Adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) | Safety and efficacy in children have not been established. | Tablet:<br>500 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | whose hyperglycemia cannot be controlled by diet alone:<br>Tablet: initial, 1 to 2 g/day; maintenance, 0.25 to 3 g/day; maximum, 3 g/day | | |
| **Combination Products** | | | |
| Glipizide and metformin | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: dosage must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20-2,000 mg | Safety and efficacy in children have not been established. | Tablet:<br>2.5-250 mg<br>2.5-/500 mg<br>5-500 mg |
| Glyburide, micronized and metformin | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus:<br>Tablet: dosage must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20-2,000 mg | Safety and efficacy in children have not been established. | Tablet:<br>1.25-250 mg<br>2.5-500 mg<br>5-500 mg |

QD=once daily

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the sulfonylureas are summarized in Table 9.

**Table 9. Comparative Clinical Trials with the Sulfonylureas**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Type 2 Diabetes – Monotherapy** | | | | |
| United Kingdom Prospective Diabetes Study Group[25] (1998)<br><br>Chlorpropamide 100 to 500 mg daily<br><br>vs<br><br>glibenclamide* 2.5 to 20 mg daily<br><br>vs<br><br>glipizide 2.5 to 40 mg daily<br><br>vs<br><br>insulin<br><br>vs<br><br>conventional therapy with diet | RCT<br><br>Patients newly diagnosed with type 2 diabetes, baseline $HbA_{1c}$ 7.05% in the dietary treatment group and 7.09% in the intensive therapy group | N=3,867<br><br>10 years | Primary:<br>Time to the first occurrence of any diabetes-related endpoint, time to diabetes-related death, all-cause mortality<br><br>Secondary:<br>MI, sudden death, stroke, amputation or death due to peripheral vascular disease, microvascular complications, retinopathy, vitreous hemorrhage, and/or fatal or nonfatal renal failure | Primary:<br>There was a 12% risk reduction (95% CI, 1 to 21; P=0.029) for any diabetes-related end point, 10% risk reduction (95% CI, -11 to 27; P=0.34) for any diabetes-related death, and a 6% risk reduction (95% CI, -10 to 20; P=0.44) for all-cause mortality when intensive therapy (sulfonylurea or insulin) was compared to conventional therapy with diet.<br><br>Patients receiving an intensive treatment (sulfonylurea or insulin) had a 25% risk reduction (95% CI, 7 to 40; P=0.0099) in microvascular end points compared to conventional therapy with diet. Most of this reduction was due to fewer cases of retinal photocoagulation.<br><br>There were no differences between the intensive and conventional treatment groups or between the three intensive treatment groups in the number of patients who had a silent MI, cardiomegaly, evidence of peripheral vascular disease, or absent peripheral pulses.<br><br>Secondary:<br>There was no significant difference between chlorpropamide, insulin, and glibenclamide in macrovascular events.<br><br>There was no significant difference between the three intensive treatments in microvascular end points or in the risk reduction for retinal photocoagulation. |
| Feinbock et al.[26] (2003) | MC, OL, PG, RCT<br><br>Patients from 36 to | N=219<br><br>20 weeks | Primary:<br>Number of responders in each | Primary:<br>Glimepiride treatment was associated with a significant responder rate compared to acarbose, 61 vs 34% respectively (P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Glimepiride 1 to 6 mg QD<br><br>vs<br><br>acarbose 50 to 200 mg TID | 80 years of age with type 2 diabetes uncontrolled on diet alone, with an $HbA_{1c}$ ≥7.8%, and a BMI 24 to 35 kg/m$^2$ | | group (defined as a FPG ≤7.8 mmol/L at the final visit)<br><br>Secondary:<br>Changes in $HbA_{1c}$, weight, PPG, and C-peptide levels from baseline | Glimepiride resulted in significant decreases in $HbA_{1c}$ (2.5±2.2%) as compared to acarbose (1.8±2.2%; P=0.014).<br><br>Secondary:<br>FPG levels were significantly decreased with glimepiride as compared to acarbose (2.6±2.6 mmol/L vs 1.4±2.8 mmol/L; P=0.004).<br><br>There was a greater reduction in $HbA_{1c}$ in the glimepiride group (2.5±2.2%) compared to the acarbose group (1.8±2.2%; P=0.014).<br><br>Decreased glucose response to breakfast was significant for glimepiride compared to acarbose (P=0.0001).<br><br>Weight loss was observed in the acarbose group (P=0.001) and glimepiride group (P=0.8) from baseline.<br><br>C-peptide levels were higher in the glimepiride group compared to the acarbose group at study end point (5.44±2.26 ng/mL vs 4.57±1.93 ng/mL; P=0.0004; intra-individual difference: 0.53±1.7 ng/mL vs –0.31±1.72 ng/mL; P=0.002). |
| Martin et al.[27] (2003)<br><br>Glimepiride<br><br>vs<br><br>glibenclamide* | MC, OS<br><br>Drug treatment-naïve patients ≥35 years of age with a confirmed type 2 diabetes diagnosis who with or without dieting received initial dose adjustment with glimepiride or glibenclamide during the study period from April 1998 to March | N=520<br><br>1 year ±3 months | Primary:<br>Mean change in body weight and BMI<br><br>Secondary:<br>Changes in $HbA_{1c}$, FPG, cholesterol | Primary:<br>Both treatments led to significant reductions in body weight and BMI over the observed treatment period as compared to baseline (P<0.01).<br><br>Mean weight loss from baseline to end point was greater with glimepiride compared to glibenclamide (-2.04±3.99 vs -0.58±3.65 kg, respectively; P<0.001). The variability of the changes between centers was significant (P<0.001), the differences between the treatment arms in change in body weight from baseline was still significant (P=0.027) if the centers were taken into account as an additional factor. Glimepiride achieved a greater reduction in BMI compared to glibenclamide over the observed period (-0.72±1.38 vs<br>-0.20±1.28 kg/m$^2$, respectively; P<0.001).<br><br>Secondary:<br>There were significant decreases from baseline in FPG and $HbA_{1c}$ from |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | 1999, disease duration <5 years, BMI ≥27 kg/m$^2$, patients before or during the study were not taking any antidiabetic medications other than glimepiride or glibenclamide or any other medication known to influence body weight | | | baseline for both groups (P<0.001). The mean change from baseline for $HbA_{1c}$ was -1.23±0.09% for glimepiride and -1.26±0.09% for glibenclamide. The mean change from baseline for FPG was -2.43±0.24 mmol/L for glimepiride and -3.03±0.24 mmol/L for glibenclamide.<br><br>Changes from baseline for TC were significant for both groups (P<0.001). The change was -0.31±0.06 mmol/L for glimepiride and -0.29±0.06 mmol/L for glibenclamide.<br><br>Change from baseline for HDL-C were 0.07±0.02 mmol/L for glimepiride (P=0.004) and -0.02±0.04 mmol/L for glibenclamide (P=0.924).<br><br>Change from baseline for LDL-C was -0.21±0.06 mmol/L for glimepiride (P=0.001) and -0.33±0.07 mmol/L for glibenclamide (P<0.001).<br><br>Change from baseline for TG was -0.03±0.12 mmol/L for glimepiride (P=0.111) and -0.29±0.09 mmol/L for glibenclamide (P<0.001). |
| Garber et al.[28] (2009)<br>LEAD-3<br><br>Liraglutide 1.2 and 1.8 mg SC QD<br><br>vs<br><br>glimepiride 8 mg/day | AC, DB, DD, MC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 | N=746<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported QOL | Primary:<br>Decreases in $HbA_{1c}$ were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; P<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; P=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; P=0.0046).<br><br>Secondary:<br>Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (P values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks.<br><br>Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; P=0.027 and 1.8 mg, -1.42 mmol/L; P=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L).<br><br>Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | months; and $HbA_{1c}$ 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy) | | | glimepiride; P=0.1616, liraglutide 1.8 mg vs glimepiride; P=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; P=0.1319).<br><br>Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (P=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (P<0.0118). Mean DBP decreased but not significantly with any treatment.<br><br>HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (P=0.0249 and P=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride).<br><br>Patients receiving liraglutide 1.8 mg reported improved QOL scoring for physical and emotional domains compared to glimepiride (P=0.02). Improvements were largely as a result of improvements in weight image and weight concern (P<0.01). |
| Garber et al.[29] (2011)<br>LEAD-3<br><br>Liraglutide 1.2 mg and 1.8 mg SC QD<br><br>vs<br><br>glimepiride 8 mg/day | ES (LEAD-3[28])<br><br>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 | N=440<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP | Primary:<br>The decrease in $HbA_{1c}$ was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; P=0.0376) and 1.8 mg (-1.1 vs -0.6%; P=0.0016) compared to glimepiride over two years of treatment.<br><br>Secondary:<br>Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; P<0.001 for both comparisons).<br><br>Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (P=0.0015 and P=0.0001, respectively).<br><br>In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (P=0.0451 for liraglutide 1.2 mg vs glimepiride). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | months; and $HbA_{1c}$ 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy) | | | The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (P values not reported).<br><br>After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (P values not reported).<br><br>No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment. |
| Bode et al.[30] (2010)<br>LEAD-3<br><br>Liraglutide 1.2 and 1.8 mg SC QD<br><br>vs<br><br>glimepiride 8 mg/day | Post-hoc analysis (LEAD-3[28])<br><br>Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months and $HbA_{1c}$ 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering | N=746<br><br>52 weeks | Primary:<br>Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive functioning and health<br><br>Secondary:<br>Not reported | Primary:<br>Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point "my weight is just right" was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (P=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; P<0.0001 and liraglutide 1.8 mg; P<0.001).<br><br>Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either "somewhat" or "very overweight" vs "just right", "somewhat underweight," or "very overweight" during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; P value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being "somewhat worried", "very worried," or "extremely worried" vs "a little concerned" or "not concerned at all" about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; P value not reported).<br><br>There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any of the cognitive functioning and performance scales during treatment (P values not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | agent monotherapy) | | | The health-related QOL composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (P=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (P<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (P values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (P=0.006).<br><br>Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (P<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses.<br><br>Decreases in $HbA_{1c}$ corresponded to improvements in general perceived health (P<0.0001), cognitive functioning composite score (P=0.006), and cognitive performance (P=0.004). Correlations of change in $HbA_{1c}$ within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg.<br><br>Secondary:<br>Not reported |
| Gottschalk et al.[31] (2007)<br><br>Glimepiride 1 to 8 mg QD<br><br>vs<br><br>metformin 500 to 1,000 mg BID | AC, MC, PG, RCT, SB<br><br>Pediatric subjects 8 to 17 years of age with type 2 diabetes ($HbA_{1c}$ >7.1 and <12.0%) with inadequate control despite treatment with either diet and | N=285<br><br>24 weeks | Primary:<br>Mean change in $HbA_{1c}$ from baseline to week 24<br><br>Secondary:<br>Mean change in $HbA_{1c}$ from baseline to week 12, proportion of | Primary:<br>Significant reductions from baseline $HbA_{1c}$ were seen in both the glimepiride (−0.54%, P=0.001) and metformin (−0.71%, P=0.0002) groups. No significant differences were observed between groups in reductions in $HbA_{1c}$.<br><br>Secondary:<br>Significant reductions in the adjusted mean change from baseline $HbA_{1c}$ to week 12 were –0.69 and –0.76% in patients receiving glimepiride and metformin, respectively (P<0.05). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | exercise alone for at least 2 weeks prior to randomization or diet and exercise combined with 3 months of ongoing or previous oral antidiabetic monotherapy | | patients achieving an $HbA_{1c}$ <7.0% at week 24, mean change in fasting self monitoring blood glucose from baseline to weeks four, eight, 12, 18, and 24, mean changes in serum lipid concentrations from baseline to week 24 and changes in BMI, safety, adverse events, hypoglycemic episodes and vital signs | A total of 42.4 and 48.1% of patients in the glimepiride and metformin groups, respectively, achieved $HbA_{1c}$ <7.0% at week 24 (P=0.347).<br><br>Significant reductions were seen in fasting self monitoring blood glucose levels from baseline to weeks 18 and 24 in patients receiving metformin (P<0.05) but no similar reductions were reported in the glimepiride group.<br><br>There were no significant differences between the glimepiride and metformin groups in the mean change from baseline in any of the serum lipid concentrations.<br><br>Significant between-group differences were observed in the mean change from baseline BMI to week 24. Values were 0.26 $kg/m^2$ and 0.33 $kg/m^2$ in patients receiving glimepiride and metformin, respectively (P=0.003).<br><br>No deaths occurred during the study. The proportions of patients experiencing ≥1 adverse event were comparable between both treatment groups, with the most common adverse events being hyperglycemia, upper abdominal pain, diarrhea, nausea and headache. Two patients experienced serious adverse events that were considered possibly related to treatment: one patient in the glimepiride group had hyperglycemia, diabetic ketoacidosis and increased serum osmolarity and one patient in the metformin group had a non-hypoglycemic convulsion.<br><br>The incidence of clinically relevant hypoglycemia was similar in both groups (P=0.554).<br><br>No clinically significant differences in vital signs were seen between treatment groups. |
| Go et al.[32] (2004)<br><br>Glipizide XL 5 to 20 mg QD in the morning<br><br>vs | DB, PC, RCT<br><br>Patients 30 to 80 years of age with a documented diagnosis of type 2 diabetes for ≥6 months prior to the | N=42<br><br>8 weeks | Primary:<br>Change from baseline in hepatic glucose production<br><br>Secondary:<br>Changes in fasting and 24 hour | Primary:<br>Hepatic glucose production in the patients receiving glipizide XL in the morning (P<0.05) or glibenclamide (P<0.01) was significantly reduced at the end of the study compared to baseline. There were no significant differences in hepatic glucose production found when comparing glipizide XL in the morning, glipizide XL in the evening, and glibenclamide.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| glipizide XL 5 to 20 mg QD in the evening<br><br>vs<br><br>glibenclamide* 5 to 20 mg QD in the morning<br><br>vs<br><br>placebo | study and who had been treated with diet alone and/or sulfonylureas for at least 2 months | | glucose and insulin, fructosamine, $HbA_{1c}$ | Fasting and 24 hour glucose were significantly reduced from baseline to a similar degree by glipizide XL in the morning (33%; P<0.001, 39%; P<0.0001, respectively), glipizide XL in the evening (33%; P<0.0001, 32%; P<0.0001), and glibenclamide (37%; P<0.05, 37%; P<0.0001).<br><br>Fructosamine and $HbA_{1c}$ were significantly reduced from baseline by glipizide XL in the morning (28%; P<0.001, 22%; P<0.0001, respectively), glipizide XL in the evening (25%; P<0.005, 24%; P<0.005), and glibenclamide (17%; P<0.001, 14%; P<0.05). Each active treatment group improved glycemic control and resulted in beneficial effects on fructosamine and $HbA_{1c}$. |
| Birkeland et al.[33] (1994)<br><br>Glipizide<br><br>vs<br><br>glyburide<br><br>vs<br><br>placebo | DB, PC, PRO, RCT<br><br>Patients with non-insulin-dependent diabetes (type 2) mellitus | N=46<br><br>15 months | Primary:<br>Changes in $HbA_{1c}$, PPG, fasting and postprandial insulin levels<br><br>Secondary:<br>Not reported | Primary:<br>There was a comparable reduction in $HbA_{1c}$ by both active treatments compared to placebo throughout the study. There was a marked initial decrease in the glipizide and glyburide groups, but all three groups showed gradually increasing $HbA_{1c}$ levels.<br><br>Glipizide and glyburide achieved and maintained lower PPG levels and increased fasting and postprandial insulin levels compared to placebo.<br><br>Secondary:<br>Not reported |
| Burge et al.[34] (1998)<br><br><u>Week 1</u><br>Placebo<br><br><u>Week 2</u><br>glipizide XL 10 mg every morning<br><br>vs | DB, PC, PRO, RCT<br><br>Patients 55 to77 years of age with type 2 diabetes treated with oral sulfonylureas alone for ≥2 months | N=58<br><br>3 weeks | Primary:<br>Development of hypoglycemia during the final nine hours of the 23-hour fast<br><br>Secondary:<br>Changes in plasma glucose, C-peptide, glucagon, | Primary:<br>No hypoglycemia occurred during any of the fasting studies.<br><br>Secondary:<br>Plasma glucose was significantly decreased from baseline when comparing all active treatments to placebo (P<0.001). When the dose of each agent was doubled, an additional decrease of plasma glucose was observed. Plasma glucose parameters did not differ between the two sulfonylureas.<br><br>Mean and peak C-peptide levels were significantly increased compared to |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| glyburide 10 mg every morning<br><br>Week 3<br>glipizide XL 20 mg every morning<br><br>vs<br><br>glyburide 20 mg every morning | | | catecholamine concentrations | placebo for both treatment groups at the 10 and 20 mg doses. Mean C-peptide concentration were increased in the glyburide group compared to the glipizide XL group during the 20 mg study (P=0.05).<br><br>Concentrations of glucagon and norepinephrine did not differ according to treatment group or dosage. There were no differences in plasma epinephrine concentrations according to treatment group. Baseline and nadir levels of epinephrine did not differ from placebo with active treatment. Mean and peak levels of epinephrine were significantly increased compared to placebo during both the 10 and 20 mg studies when the treatment groups were combined (P<0.001). There was no difference in epinephrine response between the 10 mg and 20 mg studies. |
| Chung et al.[35] (2002)<br><br>Glipizide 10 mg BID<br><br>vs<br><br>glipizide XL 20 mg QD | OL, RCT, XO<br><br>Patients 42 to 71 years of age with type 2 diabetes with no significant history of hepatic, renal, gastrointestinal, or cardiovascular disease, who were not receiving β-blockers at the time of the study and who had not received insulin for a period of more than 1 week in the 3 months before the study | N=25<br><br>1 month | Primary:<br>Changes in pharmacokinetic parameters, serum glucose, insulin, and C-peptide levels<br><br>Secondary:<br>Not reported | Primary:<br>For each tablet formulation, plasma glipizide concentrations at the start ($C_0$) and end ($C_{24}$) of the dosage interval on the fifth day were not significant (P>0.05).<br><br>At two hours after the morning and evening doses of glipizide, plasma glipizide concentrations were two to four times higher with the glipizide XL at the same times.<br><br>Mean glipizide maximum concentrations after glipizide were significantly higher after glipizide XL (P≤0.05). Relative bioavailability was 100% for glipizide doses and 81±22% for glipizide XL.<br><br>Glipizide and glipizide XL had similar effects on serum glucose levels, serum insulin levels, and C-peptide levels.<br><br>Secondary:<br>Not reported |
| Hseih et al.[36] (2006)<br><br>Glipizide XR 10 mg daily | DB, DD, PC, PG, RCT<br><br>Chinese patients 30 to 70 years of age | N=57<br><br>12 weeks | Primary:<br>Change in fasting plasma glucose<br><br>Secondary: | Primary:<br>In the intent-to-treat analysis, the mean changes in FPG between groups were not significantly different (P value not reported).<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>glipizide 5 mg BID | with type 2 diabetes for ≥6 months and maintenance of stable diet and treatment with a sulfonylurea drug regimen for the previous 3 months | | Change in $HbA_{1c}$ | In the intent-to-treat analysis, the mean changes in $HbA_{1c}$ between groups were not significantly different (P value not reported). |
| Kitabchi et al.[37] (2000)<br><br>Glipizide daily<br><br>vs<br><br>glyburide daily | PRO, RCT<br><br>Patients with type 2 diabetes who were unresponsive to diet therapy | N=18<br><br>15 months | Primary:<br>Changes in FPG, two-hour PPG after a standard breakfast, insulin and glucose response to test meal challenge, $HbA_{1c}$, glucose tolerance<br><br>Secondary:<br>Not reported | Primary:<br>Similar doses of glipizide (11 mg/day) or glyburide (10 mg/day) resulted in comparable reduction of FPG and $HbA_{1c}$. Additionally, there was an increase in first phase insulin response to intravenous glucose tolerance testing.<br><br>The reduction in FPG and two-hour PPG was greater with glipizide compared to glyburide in six months. Results demonstrated that glipizide and glyburide are equipotent at similar doses in controlling hyperglycemia in type 2 diabetes.<br><br>Secondary:<br>Not reported |
| Scott et al.[38] (2007)<br><br>Sitagliptin 5 mg BID<br><br>vs<br><br>sitagliptin 12.5 mg BID<br><br>vs<br><br>sitagliptin 25 mg BID | AC, DB, PC, RCT<br><br>Type 2 diabetics 21 to 75 years of age, inadequately controlled ($HbA_{1c}$ 7.9%) with diet and exercise | N=743<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, mean daily glucose, and body weight; adverse effects<br><br>Secondary:<br>Not reported | Primary:<br>Sitagliptin (-0.38 to -0.77%) significantly decreased $HbA_{1c}$ compared to placebo ($P<0.001$). Sitagliptin 50 mg achieved the greatest decrease. The placebo subtracted difference in $HbA_{1c}$ of glipizide was -1.00%.<br><br>Sitagliptin significantly decreased FPG and mean daily glucose compared to placebo (P values not reported).<br><br>There was no difference between sitagliptin and placebo with changes in body weight. Glipizide resulted in a modest weight gain compared to placebo (no P value reported).<br><br>The incidence of hypoglycemia was highest with glipizide (17%) compared to placebo (2%) and sitagliptin (0 to 4%, not dose-dependent).<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| vs<br><br>sitagliptin 50 mg BID<br><br>vs<br><br>glipizide 5 to 20 mg daily<br><br>vs<br><br>placebo | | | | Not reported |
| Chan et al.[39] (2008)<br><br><u>Phase I</u><br>Sitagliptin 25 to 50 mg once daily<br><br>vs<br><br>placebo<br><br><u>Phase II</u><br>Glipizide 2.5 to 20 mg daily and placebo<br><br>vs<br><br>sitagliptin 25 to 50 mg daily and placebo | DB, PC, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes, baseline $HbA_{1c}$ 6.5 to 10.0%, and renal insufficiency | N=91<br><br>54 weeks (Phase I was 12 weeks; Phase II was 42 weeks) | Primary:<br>Safety and tolerability<br><br>Secondary:<br>Efficacy | Primary:<br>Adverse events were similar among patients receiving sitagliptin and placebo/glipizide, including serious adverse events (30.8 and 38.5%, respectively), drug-related serious adverse events (1.5 and 0.0%, respectively), and adverse events leading to discontinuation.<br><br>Incidences of adverse events by body systems and specific clinical adverse events were also similar between the sitagliptin and placebo/glipizide groups, with the exception of hypoglycemia and anemia. Hypoglycemia occurred in 4.6% of patients receiving sitagliptin and 23.1% of patients receiving placebo/glipizide. Anemia occurred in 3.1% of patients receiving sitagliptin and 15.4% of patients receiving placebo/glipizide.<br><br>There was a higher incidence of MI (4.6 and 0.0%) and heart failure (7.7 and 3.8%) in the sitagliptin group compared to the placebo/glipizide group, respectively. The number of patients experiencing cardiovascular events per 100 patient-years was similar between groups.<br><br>There were six deaths (7.7%) in the sitagliptin group and one death (3.8%) in the placebo/glipizide group. This represents an overall mortality rate of 7.3 deaths per 100 patient-years, with 8.8 and 4.0 deaths per 100 patient-years in the sitagliptin and placebo/glipizide groups, respectively.<br><br>No clinically meaningful differences were observed for laboratory safety |

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| | | | | measures, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase, uric acid, electrolytes, white blood cell count or absolute neutrophil count between groups.<br><br>At week 54, the mean change from baseline in serum creatinine for patients with moderate renal insufficiency was -0.02 and 0.69 mg/dL in the sitagliptin and placebo/glipizide groups, respectively.<br><br>At week 54, small (2 mm Hg) mean decreases in systolic, diastolic and mean arterial BPs were observed for patients on sitagliptin compared to those on placebo/glipizide.<br><br>At week 54, there was a small mean decrease in body weight from baseline in the sitagliptin group (-0.9 kg) compared with no mean change in the placebo/glipizide group (0.0 kg).<br><br>Secondary:<br>At week 12, the mean change from baseline in $HbA_{1c}$ was -0.6% (95% CI, -0.8 to -0.4) in the sitagliptin group compared with -0.2% (95% CI, -0.4 to 0.1) in the placebo group<br><br>At week 12, the mean change from baseline in FPG was -25.5 mg/dL (95% CI, -38.2 to -12.8) with sitagliptin and -3.0 mg/dL (95% CI, -15.7 to 9.6) with placebo.<br><br>At week 54, the mean and least squares mean change from baseline in $HbA_{1c}$ with sitagliptin was -0.7% in the prespecified analysis and in the ANCOVA analysis. The mean and least squares mean changes from baseline were -1.0 and -0.8%, respectively in the placebo/glipizide group. Between-group testing for efficacy was not performed at the week 54 time point.<br><br>At week 54, the mean percent changes in lipids were as follows for sitagliptin: TC (+4.3%; 95% CI, -1.5 to 10.1), LDL-C (+11.9%; 95% CI, 1.6 to 22.2), and non-HDL-C (+7.1%; -1.2 to 15.3), TG (-0.7%; 95% CI, -13 to 11.5), and HDL-C (+0.9%; 95% CI, -5.9 to 7.7). The mean percent changes in lipids in the placebo/glipizide group were as follows: TC (- |

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| | | | | 0.2%; 95% CI, -10.5 to 10), LDL-C (3.3%; 95% CI, -8.6 to 15.2), non-HDL-C (-1.6%; 95% CI, -13.7 to 10.5), TG (+0.9%; 95% CI, -27.5 to 29.3), and HDL-C (+6.6%; 95% CI, -5 to 18.2). |
| Sami et al.[40] (1996)<br><br>Glyburide 20 mg daily in two divided doses<br><br>vs<br><br>glipizide 40 mg daily in two divided doses | RCT<br><br>Patients 43 to 73 years of age with non-insulin-dependent (type 2) diabetes mellitus for 5 to 15 years who manifested secondary failure to a first generation sulfonylurea (19 patients on chlorpropamide and 36 patients on tolazamide) while attending a diabetes clinic were randomly changed, at the discretion of the caring physician at the clinic | N=55<br><br>6 months | Primary:<br>Changes in body weight, FPG, $HbA_{1c}$, serum lipid profiles<br><br>Secondary:<br>Not reported | Primary:<br>Body weight, FPG, $HbA_{1c}$ levels, and lipid profiles were not significantly changed following the change over from the first generation agents (chlorpropamide and tolazamide) to second generation agents (glyburide and glipizide) in all patients, irrespective of the specific first and second generation agents given. Additionally, these values were not significantly changed when the patients were divided into two groups according to the second generation agent used.<br><br>There were no significant changes (P<0.5) in the levels of FBG and $HbA_{1c}$ in the patients following the change over to glipizide. FPG was 211±34 mg/L and $HbA_{1c}$ was 11.7±1.8% compared to 209±31 mg/L and 12.3±2.1% respectively, obtained following treatment with the first generation agents (chlorpropamide and tolazamide).<br><br>There were no significant changes (P>0.5) observed in the patients changed over to glyburide. FPG was 184±20 mg/dL and $HbA_{1c}$ was 11.0±1.4% following the change over from the first generation agents (chlorpropamide and tolazamide). Prior to the change over, FPG was 180±16 mg/dL and $HbA_{1c}$ was 11.2±1.6%.<br><br>Lipid concentrations were not significantly changed in either groups following the change over to glyburide or glipizide when compared to prior treatment with the first generation agents.<br><br>There were no significant changes in the metabolic values when the glyburide and glipizide groups were further subdivided according to the specific first generation agent used.<br><br>Secondary:<br>Not reported |
| Hollander et al.[41] (2003) | DB, MC, PC, RCT<br><br>Patients 32 to 75 | N=152<br><br>8 weeks | Primary:<br>Change from week 0 to week eight | Primary:<br>At week eight, FPG was reduced more with glyburide compared to nateglinide |

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| Nateglinide 120 mg TID before each meal<br><br>vs<br><br>glyburide 5 to 10 mg QD<br><br>vs<br><br>placebo | years of age with type 2 diabetes ≥3 months prior to entry into the trial on diet modification alone for ≥4 weeks before initial visit, mean $HbA_{1c}$ 6.8 to 11.0%, and a BMI 20 to 35 $kg/m^2$ | | during liquid meal challenges in FPG, fasting insulin, fasting C-peptide, and fasting proinsulin<br><br>Secondary:<br>Not reported | (-1.9 mmol/L; P<0.001).<br><br>Nateglinide treatment did not have significant changes from baseline with fasting levels of C-peptide, insulin, or proinsulin.<br><br>Glyburide treatment increased fasting C-peptide vs placebo and nateglinide (P<0.001), fasting insulin vs placebo (P<0.001) and nateglinide (P<0.05), and proinsulin vs placebo (P<0.001) and nateglinide (P<0.025).<br><br>Reduction of mealtime glucose excursions from nateglinide was approximately twice that from glyburide (-4.94±0.74 vs -2.71±0.71 mmol/hr/L; P<0.03).<br><br>The insulin secretion reflected by the C-peptide AUCs was approximately twice that in the glyburide group than in the nateglinide group (1.83±0.24 vs 0.95±0.23 nmol/hr/L, respectively; P=0.063 vs nateglinide).<br><br>Secondary:<br>Not reported |
| Kahn et al.[42] (2006)<br><br>Glyburide 2.5 to 7.5 mg BID<br><br>vs<br><br>metformin 500 to 1,000 mg BID<br><br>vs<br><br>rosiglitazone 4 mg QD to 4 mg BID | DB, MC, RCT<br><br>Recently diagnosed (within 3 years) type 2 diabetic patients between the ages of 30 to 75 years who had not received previous pharmacologic treatment, with FPG levels ranging from 126 to 180 mg/dL while their only treatment was lifestyle management | N=4,360<br><br>4 to 6 years (median treatment durations 3.3 years for glyburide and 4 years for rosiglitazone and metformin) | Primary:<br>Time from randomization to treatment failure (defined as FPG >180 mg/dL on consecutive testing after at least six weeks of treatment at the maximum tolerated dose)<br><br>Secondary:<br>Time from randomization to a confirmed FPG >140 mg/dL after | Primary:<br>At five years, 15% of patients receiving rosiglitazone, 21% of those on metformin, and 34% of those on glyburide had failed monotherapy. This represents a risk reduction of 32% for rosiglitazone as compared with metformin and 63% for rosiglitazone as compared with glyburide (P<0.001 for both comparisons).<br><br>Secondary:<br>Progression to a confirmed FPG ≥140 mg/dL was seen in 79 of 511 patients in the rosiglitazone group as compared with 127 of 520 patients in the metformin group (P=0.002) and 160 of 480 patients in the glyburide group (P<0.001).<br><br>At the 4-year evaluation, 40% of the patients in the rosiglitazone group achieved an $HbA_{1c}$ <7.0% compared with 36% of the patients in the metformin group (P=0.03) and 26% of the patients in the glyburide group (P<0.001). |

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| | | | at least six weeks of treatment at the maximum tolerated dose (for patients who entered the study with FPG ≤140 mg/dL); also FPG, $HbA_{1c}$, weight, measures of insulin sensitivity, β-cell function, and adverse events | The annual rate of β-cell function decline after 6 months was greatest in the glyburide group (6.1% decreased), followed by the metformin group (3.1% decreased) and rosiglitazone group (2.0% decreased) (P<0.001 for rosiglitazone vs glyburide and P=0.02 for rosiglitazone vs metformin).<br><br>Over a period of five years, the mean weight increased in the rosiglitazone group but decreased in the metformin group. In the glyburide group, weight gain occurred in the first year then remained stable.<br><br>Treatment with glyburide group was associated with lower risk of cardiovascular events (including congestive heart failure) than was seen in the rosiglitazone and metformin groups (P<0.05). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide, but fewer gastrointestinal events were reported with rosiglitazone compared to metformin and fewer hypoglycemic events were seen with rosiglitazone compared to with glyburide (P<0.001 for all comparisons). |
| Giles et al.[43] (2008)<br><br>Glyburide 10 to 15 mg daily<br><br>vs<br><br>pioglitazone 30 to 45 mg QD<br><br>Insulin was the only rescue medication allowed. | DB, MC, RCT<br><br>Patients ≥18 years of age with type 2 diabetes, $HbA_{1c}$ ≥7.0%, BMI ≤48 kg/m$^2$, NYHA functional Class II/III heart failure, left ventricular systolic dysfunction (≤40%), and receiving sulfonylurea therapy (+/- insulin) for ≥30 days before screening or discontinued metformin therapy | N=518<br><br>6 months | Primary:<br>Heart failure progression (defined as the composite of cardiovascular mortality and hospitalization or emergency room visit for heart failure) and metabolic parameters.<br><br>Secondary:<br>Not reported | Primary:<br>Pioglitazone was associated with a higher incidence rate of the composite end point compared with glyburide (13.4 vs 8.2%, respectively; P=0.024).<br><br>Death from cardiovascular cause was similar between the treatment groups (1.9 and 2.3% for pioglitazone and glyburide, respectively).<br><br>Overnight hospitalization for heart failure was higher in the pioglitazone group (9.9%) compared to glyburide group (4.7%).<br><br>Emergency room visits for heart failure occurred in 1.5% of pioglitazone patients compared to 1.2% of glyburide patients.<br><br>Echocardiographic data demonstrated preserved cardiac function with similar changes in the left ventricular mass index (P=0.959) and left ventricular ejection fraction (P=0.413) among the treatment groups. Cardiac index was significantly increased with pioglitazone compared with glyburide (P=0.012). |

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| | within 30 days of screening | | | FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment. By week 16, a significant difference in mean FPG was observed favoring pioglitazone. At week 24, pioglitazone decreased the $HbA_{1c}$ by -0.98% compared to -0.73% with glyburide (P=0.007).<br><br>At week 24, significant differences were seen between pioglitazone and glyburide in TGs (-36.8 vs +7.6 mg/dL, respectively; P<0.001), HDL-C (+4.8 vs -0.8 mg/dL, respectively; P<.001), and LDL-C (+6.9 vs -2.4 mg/dL, respectively; P<0.016).<br><br>Rates of adverse events and serious adverse events were similar between treatment groups. Hypoglycemia was more common with glyburide and edema was more common with pioglitazone. Weight gain was reported as an adverse event more frequently with pioglitazone than glyburide. (6.1 vs 2.7%, respectively). Mean weight gain was greater (2.10 vs 1.23 kg, respectively; P=0.012) with pioglitazone than with glyburide.<br><br>Secondary:<br>Not reported |
| Johnston el al.[44] (1998)<br><br>Glyburide 1.25 to 20 mg QD<br><br>vs<br><br>miglitol 25 to 50 mg TID<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Patients ≥60 years of age with type 2 diabetes treated with diet alone for ≥12 weeks, $HbA_{1c}$ 6.5 to 10.0%, and FPG >140 mg/dL | N=411<br><br>1 year | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline plasma glucose, serum insulin, and TG | Primary:<br>Mean placebo-subtracted $HbA_{1c}$ reduction from baseline was -0.50% with miglitol 25 mg TID (P<0.05 vs glyburide), -0.41% with miglitol 50 mg TID (P<0.05 vs glyburide), -0.93% for glyburide QD, and -0.01% for placebo (P<0.05 vs all active treatments).<br><br>Secondary:<br>Changes in mean plasma glucose (AUC) were +716 mg·min/dL with placebo (P<0.05 vs all active treatments), -3,361 mg·min/dL with miglitol 25 mg TID, -5,462 mg·min/dL with miglitol 50 mg TID, and -3,615 mg·min/dL with glyburide (P=0.0001 for miglitol 50 mg TID vs placebo).<br><br>Postprandial insulin levels were significantly greater with glyburide compared to placebo and miglitol (P<0.01).<br><br>Mean changes from baseline to end point for fasting TG were 1.01 with placebo and miglitol 25 mg TID, 0.98 with miglitol 50 mg TID, and one |

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| | | | | with glyburide (P=0.573 for miglitol 50 mg vs placebo).<br><br>Mean changes from baseline to end point for TG (AUC) were 1.01 with placebo, 1.03 with miglitol 25 mg TID, 1.00 with miglitol 50 mg TID, and 1.06 with glyburide (P=0.8559 miglitol 50 mg TID vs placebo).<br><br>Hypoglycemia, weight gain, and routine and serious cardiovascular events were more frequent in the glyburide group (P<0.05 vs placebo and miglitol). |
| van de Laar et al.[45] (2004)<br><br>Tolbutamide titrated 2,000 mg daily in 3 divided doses<br><br>vs<br><br>acarbose titrated to 100 mg TID | DB, RCT<br><br>Newly diagnosed patients with type 2 diabetes 40 to 70 years of age and a FPG level 6.7 to 20 mmol/L after an 8-week dietary treatment period | N=96<br><br>30 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change in fasting and post-load blood glucose and insulin levels, plasma lipids, and tolerability | Primary:<br>Both treatment groups showed a decrease in $HbA_{1c}$. The $HbA_{1c}$ change from baseline for the acarbose group was –1.1 vs -1.8% for the tolbutamide group. The difference between the groups was 0.6% in favor of tolbutamide (90% CI, 0.3 to 0.9 and 95% CI, 0.2 to 1.0).<br><br>Secondary:<br>Difference in mean decrease of FPG was 1.0 mmol/L in favor of tolbutamide (95% CI, 0.3 to 1.7).<br><br>No significant differences were seen in post-load blood glucose, fasting and post-load insulin levels, or lipids.<br><br>Significantly more patients in the acarbose group (15 vs 3) discontinued therapy because of adverse effects, mostly gastrointestinal. |
| Sullivan et al.[46] (2011)<br>FIELD<br><br>Metformin<br><br>vs<br><br>sulfonylurea<br><br>vs<br><br>diet alone | PRO<br><br>Patients with type 2 diabetes | N=6,005<br><br>5 years | Primary:<br>Cardiovascular disease outcomes<br><br>Secondary:<br>Hypoglycemic therapy | Primary:<br>Patients receiving monotherapy with either metformin or a sulfonylurea appeared to be at greater risk of cardiovascular disease compared to those on diet alone, but results were only significant for the sulfonylurea group, ranging from 42% higher risk of coronary revascularization to a doubled risk of coronary heart disease death. However, adjustment for the duration and intensity of diabetes and the severity of other cardiovascular risk factors abolished the significance of this effect. Total revascularization and total mortality were significantly higher in the sulfonylurea group compared to the metformin group, but all differences became non-significant on adjustment.<br><br>Secondary: |

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| | | | | Use of oral hypoglycemic agents increased progressively as the trial proceeded. Over five years, treatment with diet alone decreased from 31 to 15%, and dual therapy with metformin plus a sulfonylurea increased from 29 to 36%. Insulin therapy was introduced at a rate of 4% per year. Metformin monotherapy declined from 21 to 18% but the sulfonylurea monotherapy rate declined from 20 to 12%. Patients on sulfonylurea monotherapy were more likely to progress to dual therapy. |
| Simpson et al.[47] (2006)<br><br>First-generation sulfonylurea<br><br>vs<br><br>glyburide<br><br>vs<br><br>metformin | RETRO<br><br>New users of one oral diabetic agent | N=5,95<br><br>~4.6 years | Primary:<br>Mortality<br><br>Secondary:<br>Not reported | Primary:<br>An increased risk of death was associated with higher daily doses of first-generation sulfonylureas (adjusted HR, 2.1; 95% CI, 1.0 to 4.7) and glyburide (HR, 1.3; 95% CI, 1.2 to 1.4) compared to metformin (HR, 0.8; 95% CI, 0.7 to 1.1).<br><br>Secondary:<br>Not reported |
| Nichols et al.[48] (2007)<br><br>Metformin<br><br>vs<br><br>sulfonylurea<br><br>vs<br><br>insulin<br><br>vs<br><br>TZDs | MC, OS, RETRO<br><br>Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies | N=9,546<br><br>≥12 months | Primary:<br>Weight changes<br><br>Secondary:<br>Not reported | Primary:<br>Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.<br><br>Secondary:<br>Not reported |
| Gangji et al.[49] | MA (21 trials) | N=not | Primary: | Primary: |

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| (2001)<br><br>Glyburide<br><br>vs<br><br>sulfonylureas, meglitinides, insulin | Patients with type 2 diabetes | reported<br><br>Duration varied | Hypoglycemia, glycemic control, cardiovascular events, body weight, death<br><br>Secondary:<br>Not reported | Glyburide was associated with a 52% higher risk of experiencing at least one episode of hypoglycemia compared to other secretagogues (RR, 1.52; 95% CI, 1.21 to 1.92) and with an 83% higher risk compared to other sulfonylureas (RR, 1.83; 95% CI, 1.35 to 2.49).<br><br>Glyburide was not associated with a higher risk of cardiovascular events (RR, 0.84; 95% CI, 0.56 to 1.26), death (RR, 0.87; 95% CI, 0.70 to 1.07), or end-of-trial weight (95% CI, -0.4 to 3.80) compared to other secretagogues.<br><br>Secondary:<br>Not reported |
| Bolen et al.[50] (2007)<br><br>Biguanides<br><br>vs<br><br>meglitinides<br><br>vs<br><br>TZDs<br><br>vs<br><br>α-glucosidase inhibitors<br><br>vs<br><br>second-generation sulfonylureas | MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)<br><br>Patients with type 2 diabetes | N=136 (articles on intermediate outcomes)<br><br>N=167 (articles on adverse events)<br><br>N=68 (articles on micro-vascular outcomes and mortality)<br><br>Duration varied | Primary:<br>Intermediate outcomes: $HbA_{1c}$, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes<br><br>Secondary:<br>Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, | Primary:<br>Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in $HbA_{1c}$ level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.<br><br>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.<br><br>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.<br><br>Most agents except metformin increased body weight by 1 to 5 kg.<br><br>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; $P<0.05$).<br><br>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 |

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| | | | other serious adverse events | (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).<br><br>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.<br><br>Secondary:<br>According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).<br><br>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.<br><br>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.<br><br>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents. |
| Monami et al.[51] (2008)<br><br>Metformin<br><br>vs<br><br>sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists | MA<br><br>Patients with type 2 diabetes mellitus | N=7,890 (27 RCT)<br><br>Variable duration | Primary:<br>Reduction in $HbA_{1c}$ at 16 to 36 months<br><br>Secondary:<br>Not reported | Primary:<br>Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in $HbA_{1c}$ by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin.<br><br>In direct comparisons, sulfonylureas led to a greater reduction in $HbA_{1c}$ (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Not reported |
| Saenz et al.[52] (2005)<br><br>Metformin monotherapy<br><br>vs<br><br>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin | MA (29 RCTs)<br><br>Adult patients with type 2 diabetes | N=5,259<br><br>≥3 months | Primary:<br>Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photo-coagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality<br><br>Secondary:<br>Changes in $HbA_{1c}$, FPG, QOL, weight, BMI, | Primary:<br>Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).<br><br>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02).<br><br>Secondary:<br>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for $HbA_{1c}$ when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas. |

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| | | | lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow | |
| Shyangdan et al.[53] (2011)<br><br>GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)<br><br>vs<br><br>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas) | MA (RCTs)<br><br>Type 2 diabetics ≥18 years of age | N=not reported<br><br>8 to 26 weeks | Primary:<br>Change in baseline $HbA_{1c}$, incidence of hypoglycemia, weight change<br><br>Secondary:<br>Health-related QOL, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function | Primary:<br>Change in baseline $HbA_{1c}$<br>Exenatide ER significantly decreased $HbA_{1c}$ compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an $HbA_{1c}$ <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an $HbA_{1c}$ <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).<br><br>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased $HbA_{1c}$ (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in $HbA_{1c}$ compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78).<br><br>Compared to placebo, liraglutide 1.8 mg significantly decreased an $HbA_{1c}$ |

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| | | | | (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in $HbA_{1c}$ compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).<br><br>Liraglutide decreased $HbA_{1c}$ to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).<br><br>Liraglutide 1.2 mg was associated with a non-significant increase in $HbA_{1c}$ compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an $HbA_{1c}$ <7.0% compared to the 1.8 mg dose (P=0.92).<br><br>Incidence of hypoglycemia<br>The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).<br><br>Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was |

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| | | | | significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).<br><br>Weight loss<br>Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).<br><br>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).<br><br>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).<br><br>Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).<br><br>Secondary:<br>Data on mortality and morbidity were not reported for any treatment.<br><br>QOL |

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| | | | | Exenatide ER significantly improved weight-related QOL and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related QOL and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.<br><br>Data for liraglutide were not reported.<br><br>Safety<br>Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).<br><br>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.<br><br>BP<br>There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared |

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| | | | | to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.<br><br>FPG<br>There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).<br><br>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).<br><br>PPG<br>There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).<br><br>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was |

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| | | | | highly variable.<br><br>Lipid profile<br>TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.<br><br>β cell function<br>Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio. |
| Frederich et al.[54] (2010 )<br><br>Saxagliptin 2.5 to 10 mg QD<br><br>vs<br><br>glyburide, metformin, or placebo | SR (RCTs)<br><br>Inadequately controlled type 2 diabetics | N=4,607<br><br>16 to 116 weeks | Primary:<br>Composite of cardiovascular events, cardiovascular death, MI, and stroke<br><br>Secondary:<br>Not reported | Primary:<br>There were 38 (1.1%) cardiovascular events with saxagliptin compared to 23 (1.8%) with the comparator drugs (RR, 0.59; 95% CI, 0.35 to 1.00). There were 23 (0.7%) cardiovascular deaths, MIs, and stroke events with saxagliptin compared to 18 (1.4%) with the comparator drugs (RR, 0.44; 95% CI, 0.24 to 0.82). There were seven (0.2%) cardiovascular deaths with saxagliptin compared to 10 (0.8%) with comparator drugs (RR, 0.24; 95% CI, 0.09 to 0.63).<br><br>Secondary:<br>Not reported |
| Singh et al.[55] (2011)<br><br>TZDs (pioglitazone, | MA, SR (13 RCTs)<br><br>Type 2 diabetics | N=17,627<br><br>1 to 5.5 years (follow-up) | Primary:<br>Any pneumonia or lower respiratory tract infection reported as an | Primary:<br>TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or |

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| rosiglitazone)<br><br>vs<br><br>placebo, sulfonylurea, or metformin | | | adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event<br><br>Secondary:<br>Not reported | lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02).<br><br>Secondary:<br>Not reported |
| Louisa et al.[56] (2011)<br><br>TZDs (pioglitazone, rosiglitazone)<br><br>vs<br><br>placebo or other hypoglycemic agents | MA (37 RCTs)<br><br>Type 2 diabetics | N=3,000<br><br>>3 months | Primary:<br>Glycemic outcomes<br><br>Secondary:<br>Change in baseline BMI, lipid profile, BP, high-sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints | Primary:<br>Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased $HbA_{1c}$. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased HbA1c compared to placebo and a sulfonylurea.<br><br>Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose†, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea.<br><br>Secondary:<br>Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14).<br><br>Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41).<br><br>Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs. |

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| | | | | Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect.<br><br>In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in hsCRP.<br><br>Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone.<br><br>Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87). |
| Mannucci et al.[57] (2008)<br><br>Pioglitazone<br><br>vs<br><br>active comparators, placebo, no treatment | MA (94 trials)<br><br>Patients treated with pioglitazone (with or without type 2 diabetes) | N=21,180<br><br>Variable duration | Primary:<br>All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary re-vascularization), non-fatal chronic heart failure requiring hospitalization<br><br>Secondary:<br>Not reported | Primary:<br>In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported).<br><br>In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients.<br><br>In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72).<br><br>When analyzing all trials, no significant reduction of mortality was observed with pioglitazone.<br><br>Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45).<br><br>In PROactive, pioglitazone significantly reduced the incidence of non-fatal |

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| | | | | coronary events (P value not reported).<br><br>In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported.<br><br>In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23).<br><br>Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant.<br><br>In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98).<br><br>Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure.<br><br>In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance.<br><br>Secondary:<br>Not reported |
| Richter et al.[58] (2006)<br><br>Pioglitazone monotherapy (16 trials) vs acarbose (1 trial), metformin (4 trials), placebo | MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG<br><br>Adults with type 2 | 22 trials<br><br>N=6,200 randomized to pioglitazone treatment (total N not reported) | Primary:<br>Patient-oriented outcomes including mortality, morbidity and adverse effects | Primary:<br>Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). |

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| (4 trials), repaglinide (1 trial), rosiglitazone (1 trial), or a sulfonylurea (8 trials)<br><br>or<br><br>pioglitazone combination therapy vs a similar combination with another compound (9 trials including 2 trials vs rosiglitazone)<br><br>Some studies had more than one treatment arm. | diabetes, trial duration of at least 24 weeks | 24 weeks to 34.5 months | Secondary:<br>Health-related QOL and $HbA_{1c}$ | Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).<br><br>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 $kg/m^2$. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.<br><br>Secondary:<br>No study investigated health-related QOL.<br><br>Active glucose-lowering compounds like metformin, glibenclamide*, gliclazide† or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to pioglitazone treatment (P values not reported). |
| Lago et al.[59] (2007)<br><br>Pioglitazone 15 to 45 mg/day (2 trials) or rosiglitazone 4 to 8 | MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and | 7 trials<br><br>N=20,191<br><br>29.7 months (range, 12 to 48 months) | Primary:<br>Development of congestive heart failure, risk of cardiovascular death | Primary:<br>Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group.<br><br>Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or |

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| mg/day (5 trials)<br><br>vs<br><br>placebo (4 trials), glibenclamide‡ (1 trial), glimepiride (1 trial), metformin (1 trial), or metformin plus nonspecified sulfonylurea (1 trial)<br><br>Doses of comparators were not specified and 1 trial had 2 control groups. | cardiovascular death<br><br>Patients with prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m$^2$, mean baseline $HbA_{1c}$ 7.72% | | Secondary:<br>Not reported | rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07).<br><br>The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96).<br><br>Secondary:<br>Not reported |
| Nagajothi et al.[60] (2008)<br><br>Pioglitazone<br><br>vs<br><br>active comparators (metformin and/or sulfonylurea) or placebo | MA (5 trials)<br><br>Patients treated with pioglitazone | N=not reported<br><br>Duration varied | Primary:<br>MI<br><br>Secondary:<br>Stroke, revascularization, total mortality, cardiovascular mortality | Primary:<br>The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17).<br><br>Secondary:<br>The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07).<br><br>The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56).<br><br>The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11.<br><br>The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47). |
| Lincoff et al.[61] (2007)<br><br>Pioglitazone monotherapy vs | DB, MA, RCT with placebo or active comparator<br><br>Adult patients with | N=16,390 (19 trials)<br><br>4 months to 3.5 years | Primary:<br>Composite of death from any cause, MI or stroke | Primary:<br>Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| metformin (1 trial), placebo (4 trials), sulfonylureas (6 trials) or rosiglitazone (1 trial)<br><br>or<br><br>pioglitazone combination therapy (7 trials) with insulin, metformin, or sulfonylureas vs active comparator or placebo | type 2 diabetes and inadequate glycemic control | | Secondary:<br>Incidence of serious heart failure | Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09).<br><br>Progressive separation of time-to-event curves became apparent after approximately one year of therapy.<br><br>Secondary:<br>Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17). |
| Karter et al.[62] (2005)<br><br>Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies | Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001 | N=23,440<br><br>10.2 months (mean) | Primary:<br>Time-to-incident admission to hospital for congestive heart failure<br><br>Secondary:<br>Not reported | Primary:<br>Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99).<br><br>Secondary:<br>Not reported |
| Nissen et al.[63] (2007)<br><br>Rosiglitazone monotherapy or | MA of RCTs of more than 24 weeks that had outcome data for MI and death from | 42 trials<br><br>n=15,560 for rosiglitazone; n=12,283 for | Primary:<br>MI and death from cardiovascular causes | Primary:<br>Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03).<br><br>Compared to the control agent, rosiglitazone was associated with a trend |

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| combination therapy<br><br>vs<br><br>placebo or active comparators (including gliclazide†, glimepiride, glipizide, glyburide, insulin, and metformin) | cardiovascular causes (included ADOPT and DREAM trials)<br><br>Mean age of participants was 56 years, mean baseline $HbA_{1c}$ 8.2% | comparator<br><br>24 to 208 weeks | Secondary:<br>Not reported | toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06).<br><br>Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24).<br><br>Secondary:<br>Not reported |
| Singh et al.[64] (2007)<br><br>Rosiglitazone<br><br>vs<br><br>control (placebo or other non-TZD oral hypoglycemic drug including glyburide or metformin) | MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration<br><br>Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical data on all adverse events | 4 trials<br><br>N=14,291 (n=6,421 rosiglitazone; n=7,870 control)<br><br>1 to 4 years | Primary:<br>RR of MI, heart failure, and cardiovascular mortality<br><br>Secondary:<br>Not reported | Primary:<br>Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control.<br><br>There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53).<br><br>Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92).<br><br>Secondary:<br>Not reported |
| Richter et al.[65] (2007)<br><br>Rosiglitazone | MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, | 18 trials<br><br>N=3,888 randomized to | Primary:<br>Patient-oriented outcomes including | Primary:<br>No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, |

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| monotherapy (10 trials) vs glyburide (2 trials), metformin (3 trials), pioglitazone (1 trial), placebo (5 trials), or repaglinide (1 trial)<br><br>or<br><br>rosiglitazone combination therapy vs a similar combination with another compound (8 trials)<br><br>Some studies had more than 1 treatment arm. | included the ADOPT trial), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | rosiglitazone treatment (total N not reported)<br><br>24 weeks to 4 years (median 26 weeks) | mortality, morbidity and adverse effects<br><br>Secondary: Health-related QOL and metabolic control ($HbA_{1c}$) | 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference).<br><br>The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).<br><br>The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 $kg/m^2$. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).<br><br>Secondary:<br>No study investigated health-related QOL. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Active glucose-lowering compounds like metformin, glibenclamide‡ or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to rosiglitazone treatment. |
| **Type 2 Diabetes – Combination Therapy** | | | | |
| Lopez-Alvarenga et al.[66] (1999)<br><br>Chlorpropamide 500 mg daily, metformin 1,200 mg daily, and acarbose 100 mg TID<br><br>vs<br><br>chlorpropamide 500 mg daily, metformin 1,200 mg daily, and NPH insulin at bedtime<br><br>vs<br><br>chlorpropamide 500 mg daily, metformin 1,200 mg daily, and placebo | DB, RCT, XO<br><br>Patients with type 2 diabetes 35 to 70 years of age with BMI 23 to 35 $kg/m^2$, with a fasting plasma glucose above 8.8 mmol/L despite maximal doses of chlorpropamide and metformin for at least 2 months | N=46<br><br>42 weeks | Primary:<br>Change in FPG from baseline, body weight, $HbA_{1c}$, fasting insulin, fasting C-peptide, intravenous glucose tolerance test (incremental area), glucose meal tests (incremental area)<br><br>Secondary:<br>Not reported | Primary:<br>Changes in FPG from baseline were not significant for placebo (P=0.62), but were significant for acarbose (P=0.05) and insulin (P=0.003).<br><br>Changes in $HbA_{1c}$ from baseline were not significant for placebo (P=0.62) and acarbose (P=0.3), but were significant for insulin (P=0.008).<br><br>Changes in body weight were not significant in any group; P=0.2 for each group from baseline.<br><br>Changes in fasting insulin from baseline were not significant for placebo (P=0.38), but were significant for acarbose (P=0.03) and insulin (P=0.02).<br><br>Changes in fasting C-peptide from baseline were not significant in any group, placebo (P=0.7), acarbose (P=0.5), and insulin (P=0.24).<br><br>Changes in intravenous glucose tolerance test (incremental area) from baseline were not significant in any group, placebo (P=0.36), acarbose (P=0.91), and insulin (P=0.94).<br><br>Changes in glucose meal tests (incremental area) from baseline were not significant for placebo (P=0.84) and insulin (P=0.08), but were for acarbose (P=0.02).<br><br>Changes in insulin (incremental area) from baseline were not significant for any group, placebo (P=0.92), acarbose (P=0.3), and insulin (P=0.43).<br><br>Thirty-seven percent of patients developed severe bloating during acarbose use. This was significant (P<0.05) compared to acarbose and placebo or insulin.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Yokoyama et al.[67] (2011)<br><br>Continuation of glimepiride for 3 months<br><br>vs<br><br>discontinuation of glimepiride for 3 months<br><br>All patients received metformin and basal insulin. | OL, XO<br><br>Patients with type 2 diabetes ≥5 years duration who are receiving insulin, metformin, and a sulfonylurea; BMI ≤40 kg/m$^2$, and $HbA_{1c}$ ≤8.0% | N=25<br><br>6 months | Primary:<br>Plasma glucose levels, change in baseline $HbA_{1c}$<br><br>Secondary:<br>Not reported | Primary:<br>During meal tolerance tests performed at the end of each three month period, significant increases in plasma glucose were seen in patients who discontinued glimepiride at 0-, 30-, and 60-minutes, while significant decreases in serum C-peptide were observed as 60- and 120-minutes.<br><br>$HbA_{1c}$ significantly increased in patients discontinuing glimepiride (from 6.6±0.6 at baseline to 7.7±0.8 at three months; P<0.0001). Increases in $HbA_{1c}$ were closely correlated with decreases in AUC of meal-stimulated serum C-peptide (P<0.001).<br><br>Secondary:<br>Not reported |
| Dhindsa et al.[68] (2003)<br><br>Glimepiride 2 mg QD<br><br>vs<br><br>gliclazide† 80 mg BID<br><br>All patients received existing metformin regimens. | DB, RCT, XO<br><br>Patients 50 to 70 years of age with type 2 diabetes and inadequate glycemic control despite metformin 500 mg BID monotherapy | N=12<br><br>12 weeks | Primary:<br>Changes in fructosamine, augmentation index, peak microvascular response to acetylcholine and sodium nitroprusside, and $PD_{10}$ values (dose of agonist required to increase mean arterial BP by 10 mm Hg)<br><br>Secondary:<br>Not reported | Primary:<br>Metabolic control improved following the addition of a sulfonylurea, as seen by the reductions in serum fructosamine concentrations, but there were no significant differences in the antidiabetic effect between glimepiride and gliclazide as add-on therapy.<br><br>There was no change in augmentation index during treatment with either sulfonylurea.<br><br>There were no differences in pressor responsiveness ($PD_{10}$) or microvascular responses between the two treatment groups.<br><br>Secondary:<br>Not reported |
| Derosa et al.[69] | MC, RCT, SB | N=111 | Primary: | Primary: |

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| (2011)<br><br>Exenatide 5 µg SC BID, titrated up to 10 µg SC BID<br><br>vs<br><br>glimepiride 1 mg TID, titrated up to 2 mg TID | Patients ≥18 years of age with type 2 diabetes intolerant to metformin at the highest dosages (2,500 to 3,000 mg/day) | 12 months | Change in baseline body weight, glycemic control, insulin resistance<br><br>Secondary:<br>Not reported | There was decrease of body weight and BMI after six, nine, and 12 months (*P*<0.05, *P*<0.01, *P*<0.001, respectively) with exenatide, not obtained with glimepiride. BMI reached with exenatide was significantly lower compared to glimepiride (P<0.05).<br><br>A similar decrease in $HbA_{1c}$, FPG, and PPG after nine (*P*<0.05 for all), and after 12 months (*P*<0.01 for all) with both treatments, without significant differences between the two treatments.<br><br>Exenatide resulted in a reduction of fasting plasma insulin, and HOMA-IR after 12 months (*P*<0.05 for both), not observed with glimepiride; fasting plasma insulin increased with glimeperide. Values reached with exenatide were significantly lower compared to values reached with glimepiride after 12 months (*P*<0.05).<br><br>Exenatide, but not glimepiride, gave an increase of adiponectin after 12 months (*P*<0.05), and the value registered with exenatide was significantly higher compared to the value recorded with glimepiride at trial end (*P*<0.05).<br><br>A decrease of tumor necrosis factor-α was observed after 12 months (*P*<0.05) with exenatide, but no with glimepiride; furthermore the value obtained with exenatide was significantly better compared to the value obtained with glimepiride after 12 months (*P*<0.05). Exenatide, but not glimepiride, gave a reduction of high sensitivity CRP after nine and 12 months (*P*<.0.05 and *P*<0.01) compared to baseline and glimepiride (*P*<0.05).<br><br>Secondary:<br>Not reported |
| Forst et al.[70] (2010)<br><br>Linagliptin 1, 5, or 10 mg/day<br><br>vs | AC, DB, MC, PC, PG, RCT<br><br>Type 2 diabetics 21 to 75 years of age with BMI 25 to 40 kg/m$^2$, who had | N=333<br><br>12 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and body | Primary:<br>Placebo corrected decreases in $HbA_{1c}$ were -0.40±0.14 (P=0.006), -4.40±0.14 (P<0.001), and -8.00±1.50% (P<0.001) with linagliptin 1, 5, and 10 mg, respectively. Treatment with glimepiride significantly decreased $HbA_{1c}$ compared to treatment with placebo -0.68% (P<0.0001).<br><br>Secondary: |

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| placebo<br><br>vs<br><br>glimepiride (OL) 1 to 3 mg/day<br><br>Patients were also receiving metformin. | inadequate glycemic control on metformin alone ($HbA_{1c}$ 7.5 to 10.0%) | | weight, proportion of patients achieving an $HbA_{1c}$ ≤7.0%, proportion of patients with an $HbA_{1c}$ decrease ≥0.5%, safety | Decreases in FPG were significantly greater with all doses of linagliptin compared to placebo. The placebo corrected FPG decrease were -1.1 (P=0.0020), -1.9 (P<0.0001), and -1.6 mmol/L (P<0.0001) with linagliptin 1, 5, and 10 mg, respectively.<br><br>After 12 weeks a small decrease in body weight was observed with all doses of linagliptin (-0.15, -0.57, and -1.27 kg, respectively; P values not reported).<br><br>Only one (1.4%) patient receiving placebo achieved an $HbA_{1c}$ ≤7.0% compared to ten (approximately 15%), nine (approximately 15%), and 14 (21%) patients receiving linagliptin 1, 5, and 10 mg/day, respectively (P values not reported).<br><br>A greater proportion of patients receiving linagliptin achieved an $HbA_{1c}$ decrease ≥0.5% compared to patients receiving placebo (43.8 to 53.2 vs 12.9%; P value not reported). In addition, $HbA_{1c}$ decreased by ≥1.0% in 14.1, 27.4, 22.7, and 7.7% with linagliptin 1 mg, linagliptin 5 mg, linagliptin 10 mg, and placebo (P values not reported).<br><br>Linagliptin was well tolerated. The most commonly reported adverse events were considered to be of mild or moderate intensity; however, ten patients experienced severe adverse events. No episodes of hypoglycemia were reported. Three (4.6%) patients experienced hypoglycemia after dosing with glimepiride. |
| Yang et al.[71] (2011)<br><br>Liraglutide 0.6, 1.2, or 1.8 mg QD<br><br>vs<br><br>glimepiride 4 mg QD<br><br>All patients | AC, DB, DD, RCT<br><br>Adult patients with type 2 diabetes | N=929<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportions of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, body weight, BP, hypoglycemia, adverse events | Primary:<br>Baseline $HbA_{1c}$ was significantly reduced with all treatments. Treatment with liraglutide 1.2 and 1.8 mg was non-inferior to glimepiride (mean reduction: 1.36, 1.45, 1.39% points, respectively).<br><br>Secondary:<br>No significant difference was shown in the proportion of patients achieving $HbA_{1c}$ <7.0 or ≤6.5% between liraglutide 1.2 and 1.8 mg and glimepiride.<br><br>Liraglutide resulted in a mean reduction in weight of -1.8 to -2.4 kg compared to 0.1 kg weight gain with glimepiride. |

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| received metformin. | | | | Liraglutide significantly reduced SBP compared to glimepiride.<br><br>Two patients receiving glimeperide experienced major hypoglycemia compared to zero patients receiving liraglutide. Liraglutide was associated with a 10-fold lower incidence of minor hypoglycemia compared to glimeperide.<br><br>Gastrointestinal disorders were the most commonly reported adverse events with liraglutide therapy; events were transient and resulted in few withdrawals. |
| Chogtu et al.[72] (2009)<br><br>Glimepiride 2 mg daily and pioglitazone (variable doses)<br><br>vs<br><br>glimepiride 2 mg daily and rosiglitazone (variable doses) | OL, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes who received glimepiride and required a TZD due to a lack of glycemic control, normotensive, and not on antilipemic therapy | N=63<br><br>12 weeks | Primary:<br>Blood glucose levels, plasma lipids, BP<br><br>Secondary:<br>Not reported | Primary:<br>The mean change in the FPG and PPG from baseline to week 12 was significant in both groups (P<0.05). There was no significant difference between the groups with regard to the change in FPG (P=0.10) and PPG (P=0.95).<br><br>$HbA_{1c}$ levels also decreased from baseline to week 12. There was no significant difference between the treatment groups (P>0.05).<br><br>At week 12, 37.9% of patients in the pioglitazone group and 17.8% of patients in the rosiglitazone group had $HbA_{1c}$ <7.0% (P value not reported).<br><br>TC decreased in both treatment groups; however, to a greater extent with pioglitazone compared to rosiglitazone (P=0.004). TG in the pioglitazone group (P=0.0006) decreased significantly in comparison to the rosiglitazone group (P=0.255) at 12 weeks (P=0.002 pioglitazone vs rosiglitazone). LDL-C decreased significantly (P=0.005) in the pioglitazone group compared to the rosiglitazone group. There was no significant difference in HDL-C among the treatment groups (P>0.05).<br><br>There was no change in SBP with pioglitazone or rosiglitazone from baseline to week 12. There was also no significant difference in SBP between the treatment groups (P=0.45).<br><br>There was an increase in the weight following treatment with pioglitazone |

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| | | | | and rosiglitazone; however, there was no difference between the groups (P=0.10).<br><br>Secondary:<br>Not reported |
| Chou et al.[73] (2008)<br><br>Glimepiride 1mg titrated to 4 mg QD (GLIM)<br><br>vs<br><br>rosiglitazone 4 mg titrated to 8 mg QD (RSG)<br><br>vs<br><br>rosiglitazone/ glimepiride 4/1 mg titrated to 4/4 mg (regimen A) or titrated to 8/4 mg QD (regimen B) (RSG/GLIM) | DB, MC, PG, RCT<br><br>Type 2 diabetics, $HbA_{1c}$ 7.5 to 12.0%, fasting C-peptide ≥0.8 ng/mL, FPG ≥126 mg/dL, who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months | N=901<br><br>28 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, proportion of patients achieving $HbA_{1c}$ and FPG targets, HOMA-S, HOMA-B, cardiovascular biomarkers, safety | Primary:<br>Both rosiglitazone/glimepiride regimens significantly reduced $HbA_{1c}$ to a greater extent than glimepiride or rosiglitazone monotherapy regimens (P<0.0001).<br><br>Secondary:<br>A significantly greater reduction in FPG levels was observed in the rosiglitazone/glimepiride group compared to the glimepiride or rosiglitazone monotherapy groups (P<0.0001).<br><br>Significantly more patients achieved $HbA_{1c}$ target levels ≤6.5 and <7.0% with either rosiglitazone/glimepiride regimen than patients with glimepiride or rosiglitazone monotherapy regimens (P<0.0001).<br><br>Improvement in CRP was also observed in patients treated with rosiglitazone/glimepiride or rosiglitazone monotherapy compared to patients treated with glimepiride monotherapy (P<0.05).<br><br>There were no new safety or tolerability issues identified from its monotherapy components and a similar adverse event profile was observed across the fixed-dose regimens. The most commonly reported adverse event was hypoglycemia and the incidence of confirmed symptomatic hypoglycemia (3.6 to 5.5%) was comparable among subjects treated with a fixed-dose regimen and glimepiride monotherapy. |
| McCluskey et al.[74] (2004)<br><br>Glimepiride 2 to 8 mg QD and rosiglitazone (existing therapy) | MC, PC, RCT<br><br>Patients with type 2 diabetes poorly controlled ($HbA_{1c}$ 7.5 to 9.5%) with rosiglitazone monotherapy | N=40<br><br>30 weeks | Primary:<br>Effect on $HbA_{1c}$<br><br>Secondary:<br>Effect on FPG, body weight, lipoproteins, proportion of | Primary:<br>Significant reductions in $HbA_{1c}$ were observed with glimepiride (-1.2%) compared to placebo (-0.3%; P<0.001).<br><br>Secondary:<br>Significant reductions in FPG were observed with glimepiride (-24.41 mg/dL) compared to placebo (5.9 mg/dL; P<0.008). |

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| vs<br><br>rosiglitazone (existing therapy) | | | patients who achieved $HbA_{1c}$ and FPG targets | Significantly greater proportion of patients receiving glimepiride achieved the target $HbA_{1c}$ ≤7.0% (60.0 vs 14.3%; P<0.008).<br><br>There were no significant differences between treatment groups in TC, HDL-C, LDL-C, or TG at any time during study period. |
| Rosenstock et al.[75] (2008)<br><br>Study A<br>Glimepiride 3 mg QD and rosiglitazone 4 mg QD (RSG 4 mg + GLIM)<br><br>vs<br><br>glimepiride 3 mg QD and rosiglitazone 8 mg QD (RSG 8 mg + GLIM)<br><br>vs<br><br>glimepiride 3 mg QD (GLIM alone)<br><br>Study B<br>Glimepiride 2 to 4 mg QD and rosiglitazone 4 mg QD (RSG add-on)<br><br>vs<br><br>glimepiride 4 to 8 | 2 DB, PC, RCT<br><br>Patients 40 to 80 years of age (Study A) or 18 to 75 years of age (Study B) with type 2 diabetes, $HbA_{1c}$ ≥7.0% and FPG 126 to 270 mg/dL at baseline; in the 3 months prior to enrolment, eligible patients in Study A received monotherapy with an oral antidiabetic agent; eligible patients in Study B were treated with a non-TZD oral antidiabetic therapy for ≥3 months prior to screening, including metformin monotherapy, sulfonylurea monotherapy, or low-dose combination therapy with metformin and | N=174 (Study A)<br><br>N=391 (Study B)<br><br>26 weeks (Study A)<br><br>24 weeks (Study B) | Primary:<br>Mean change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients with $HbA_{1c}$ <7.0% and/or $HbA_{1c}$ reduction ≥0.7% at the end of the treatment period, mean change in baseline FPG | Study A<br>Primary:<br>At week 26, the mean change in $HbA_{1c}$ from baseline was -0.63% in the RSG 4 mg+GLIM (P=0.03 vs GLIM 3 mg), -1.17% in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -0.08% in the GLIM 3 mg group.<br><br>Secondary:<br>The mean change in FPG from baseline was -21 mg/dL in the RSG 4 mg+GLIM (P=0.09 vs GLIM alone), -43 mg/dL in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -2 mg/dL for GLIM 3 mg.<br><br>At week 26, 43% of patients achieved $HbA_{1c}$ <7.0% in the RSG 4 mg+GLIM group (P=0.0129 vs GLIM alone) and 68% achieved the same $HbA_{1c}$ goal in the RSG 8 mg+GLIM group (P=0.0001 vs GLIM 3 mg) compared to 32% in the GLIM 3 mg.<br><br>Study B<br>Primary:<br>At week 24, the mean change in $HbA_{1c}$ from baseline was -0.68% in the RSG add-on group compared to -0.08% in the GLIM 4 to 8 mg group (P<0.0001).<br><br>Secondary:<br>The mean change in FPG from baseline was -28 mg/dL in the RSG add-on group compared to -1 mg/dL in the GLIM 4 to 8 mg group (P<0.0001).<br><br>At week 24, 39% of patients achieved $HbA_{1c}$ <7.0% in the RSG add-on group compared to 15% in the GLIM 4 to 8 mg group (P<0.0001).<br><br>Insulin sensitivity increased significantly in the RSG add-on group but was unchanged with GLIM 4 to 8 mg. β-cell function increased over 24 |

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| mg QD and placebo (GLIM) | sulfonylurea | | | weeks in both treatment groups but with a significantly greater increase with RSG add-on group.<br><br>RSG add-on significantly reduced fasting levels of C-peptide (P=0.025), proinsulin (P=0.0006), and insulin (P=0.013) and reduced the proinsulin: insulin ratio (P<0.0001). There were no significant changes in any of these parameters with GLIM 4 to 8 mg (C-peptide; P=0.075, proinsulin; P=0.42, insulin; P=0.10 and proinsulin:insulin ratio; P=0.34). |
| Bao et al.[76] (2010)<br><br>Glipizide XL<br><br>vs<br><br>glipizide XL plus acarbose | AC, OL, RCT<br><br>Newly diagnosed type 2 diabetics, 30 to 70 years of age, with $HbA_{1c}$ 7.0 to 9.8%, and no prior use of antidiabetic medications | N=40<br><br>8 weeks | Primary:<br>Glycemic control, improvements in insulin secretion and sensitivity, glycemic variability, hypoglycemia<br><br>Secondary:<br>Not reported | Primary:<br>After eight weeks, FPG, two-hour post-oral glucose tolerance test plasma glucose, mean blood glucose, $HbA_{1c}$, glycated albumin, and HOMA-IR were significantly decreased with both treatments. HOMA-B increased significantly compared to baseline (P<0.01 for both). Compared to glipizide XL, combination therapy had significantly lower mean blood glucose and HOMA-IR values after eight weeks (P<0.05 for both). Mean changes in mean blood glucose, $HbA_{1c}$, and glycated albumin were all greater with combination therapy compared to monotherapy, with only differences in mean blood glucose reaching significant. The overall glucose-lowering and -stabilizing effects were more pronounced with combination therapy.<br><br>Over the duration of the trial, the decreases in mean amplitude of glycemic excursions and $AUC_{postprandial\ incremental}$ were significant with both treatments (P<0.01). There was also a significant decrease in mean of daily differences with combination therapy compared to baseline (P<0.01). Patients receiving combination therapy had significantly lower mean of daily differences, mean amplitude of glycemic outcomes, and $AUC_{postprandial\ incremental}$ values compared to patients receiving monotherapy after eight weeks (P<0.05 for all).<br><br>There were no significant between-group differences in either the frequency or the duration of hypoglycemia. The mean duration of hypoglycemia was 88.8±84.7 minute per event with monotherapy and 176.3±123.5 minute per event with combination therapy (P=0.114). Patients receiving monotherapy had 0.7±0.4 events per day compared to 0.8±0.4 events per day in patients receiving combination therapy (P=0.612). There was no difference in total instances of severe |

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| | | | | hypoglycemia reported.<br><br>Secondary:<br>Not reported |
| Goldstein et al.[77] (2003)<br><br>Glipizide 15 mg BID<br><br>vs<br><br>metformin 500 to 2,000 mg daily<br><br>vs<br><br>glipizide/ metformin 5/500 mg daily (dose titrated up to 4 tablets per day) | DB, MC, PG, RCT<br><br>Patients with type 2 diabetes and inadequate glucose control ($HbA_{1c}$ 7.5 to 12.0%) despite monotherapy with at least half the maximum labeled daily dose of a sulfonylurea, FPG <300 mg/dL, and BMI ≥25 to ≤40 $kg/m^2$ | N=247<br><br>18 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Changes in FPG, three-hour PPG, area under the concentration-time curve (AUC), three-hour postprandial insulin incremental AUC during three hours after a standard test meal, fasting insulin level, serum lipid profiles, body weight | Primary:<br>The decreases in $HbA_{1c}$ were significantly greater in the glipizide/metformin group compared to either of the monotherapy groups (P<0.001). A total of 36.6% of patients receiving glipizide/metformin, 8.9% of patients receiving glipizide, and 9.9% of patients receiving metformin had an $HbA_{1c}$ <7.0% at the final visit.<br><br>Secondary:<br>Combination therapy reduced the FPG from baseline significantly more compared to glipizide and metformin monotherapies (P<0.001).<br><br>Combination therapy controlled PPG more than metformin monotherapy or glipizide monotherapy, as measured using a three-hour incremental AUC (P=0.002, and P<0.001, respectively).<br><br>The postprandial insulin three-hour incremental AUC increased from baseline with combination therapy, and decreased with glipizide monotherapy; the differences between these groups were not significant. There was a decrease in the postprandial insulin AUC in the metformin monotherapy group, which was significant (P<0.001 vs combination group).<br><br>Fasting insulin decreased in the combination therapy group and in the metformin monotherapy group. Fasting insulin increased in the glipizide monotherapy group. The changes in the combination therapy group did not differ significantly from either monotherapy group.<br><br>There were decreases in body weight in all groups, -0.3 kg with the combination therapy group, -0.4 kg with the glipizide monotherapy group, and -2.7 kg in the metformin monotherapy group. The changes in the metformin monotherapy group were significant compared to the combination therapy group (P<0.001). |

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| | | | | There were no significant changes in the fasting lipid profile in the combination group or metformin monotherapy group. There were significant increases from baseline in TC and TG in the glipizide monotherapy group. |
| Garber et al.[78] (2002)<br><br>Glyburide 2.5 mg daily<br><br>vs<br><br>metformin 500 mg daily<br><br>vs<br><br>glyburide/ metformin 1.25/250 mg daily<br><br>vs<br><br>glyburide/ metformin 2.5/500 mg daily<br><br>vs<br><br>placebo<br><br>Doses were titrated to a maximum of 4 tablets per day. | DB, MC, PC, PG, RCT<br><br>Patients with type 2 diabetes with inadequate glycemic control with diet and exercise, $HbA_{1c}$ >7.0%, normal renal and liver function, and a BMI ≤38 $kg/m^2$ | N=806<br><br>20 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Changes in FPG, two-hour PPG, fasting and two-hour insulin levels, serum lipid concentrations, body weight | Primary:<br>Patients in both glyburide/metformin groups had significantly greater mean reduction from baseline $HbA_{1c}$ (level of 8.2%) compared to the placebo group (P<0.001). The reductions in $HbA_{1c}$ from baseline for each glyburide/metformin group were significantly greater than the placebo or metformin groups (P<0.001). The reduction in $HbA_{1c}$ in the glyburide/metformin 1.25/250 mg group was significantly greater compared to the glyburide group (P<0.016), and for the glyburide/metformin 2.5/500 mg group compared to the glyburide group (P<0.004).<br><br>Sixty-six percent of the patients in the glyburide/metformin 1.25/250 mg group (P=0.006 vs metformin) and 72% of the patients in the glyburide/metformin 2.5/500 mg group (P<0.001 vs metformin, P=0.037 vs glyburide) had achieved an $HbA_{1c}$ <7.0% compared to 60% of the patients in the glyburide group, 50%of patients in the metformin group, and 20% of patients in the placebo group.<br><br>Secondary:<br>Mean decreases in FPG concentrations were significantly greater for both combination groups compared to the placebo (P<0.001) and metformin groups (P<0.001). Mean decreases in FPG were numerically greater in both combination groups compared to the glyburide group, but the differences were not significant.<br><br>Glyburide/metformin 1.25/250 mg group, glyburide/metformin 2.5/500 mg group, and the glyburide group had modest changes in body weight of 1.4, 1.9, and 1.7 kg, respectively, compared to 0.7 and 0.6 kg mean decrease in patients receiving placebo and metformin, respectively. The mean changes in body weight for the glyburide/metformin groups and the glyburide group were significantly different from placebo.<br><br>There were no significant changes seen in TC, LDL-C, or HDL-C, and |

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| | | | | TGs with any treatment. |
| Marre et al.[79] (2002)<br><br>Glyburide 5 mg daily<br><br>vs<br><br>metformin 500 mg daily<br><br>vs<br><br>glyburide/ metformin 2.5/500 mg daily<br><br>vs<br><br>glyburide/ metformin 5/500 mg daily<br><br>Doses were titrated to a maximum of 4 tablets per day. | DB, MC, PG, RCT<br><br>Patients >18 years of age with type 2 diabetes with a FPG ≥126 mg/dL despite treatment with monotherapy metformin ≥850 mg BID or ≥500 mg TID, diet, and exercise for 2 months prior to enrollment, and BMI <40 kg/m$^2$ | N=411<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Changes in FPG, fructosamine levels | Primary:<br>Mean $HbA_{1c}$ levels improved in all groups. There were significantly greater reductions in the patients receiving combination therapy as compared to either monotherapy (P<0.05). There were no significant differences in the amount of the reductions in the $HbA_{1c}$ between the two combination therapies or the two monotherapies.<br><br>Seventy-five percent of the glyburide/metformin 2.5/500 mg group and 63.8% of the glyburide/metformin 5/500 mg group achieved an $HbA_{1c}$ <7.0% as compared to the metformin (37.6%) or glyburide (41.9%) groups (P=0.001 for both).<br><br>Secondary:<br>FPG decreased in all groups. There were significant improvements in both the combination groups compared to either monotherapy (P<0.05). There were no significant differences in effects on FPG between either of the combination therapies or the monotherapies.<br><br>Mean decreases in fructosamine in both combination groups were significantly greater (P<0.05) compared to the changes seen in the monotherapy groups. |
| DeFronzo et al.[80] (1995)<br><br><u>Protocol 1:</u><br>Metformin 850 to 2,550 mg daily<br><br>vs<br><br>placebo | 2 DB, PG, RCT<br><br>Moderately obese patients with type 2 diabetes inadequately controlled by diet (Protocol 1) or diet plus glyburide (Protocol 2) | <u>Protocol 1</u><br>N=289<br>29 weeks<br><br><u>Protocol 2</u><br>N=632<br>29 weeks | Primary:<br>Changes in plasma glucose, $HbA_{1c}$, plasma insulin, lipids, plasma lactate<br><br>Secondary:<br>Not reported | Primary:<br><u>Protocol 1:</u><br>As compared to the placebo group, the metformin group had lower mean FPG concentrations (189±5 vs 244±6 mg/dL; P<0.001). $HbA_{1c}$ levels were also lower in the metformin group (7.1±0.1 vs 8.6±0.2%; P<0.001).<br><br>The changes from baseline for TC and LDL-C for metformin were significant compared to placebo (P=0.001 and P=0.019, respectively).<br><br>Fasting plasma lactate levels were similar at all times during the active- |

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| Protocol 2:<br>Glyburide 5 to 10 mg BID<br><br>vs<br><br>metformin 500 to 2,500 mg daily<br><br>vs<br><br>glyburide plus metformin | | | | treatment in both groups.<br><br>Protocol 2:<br>Patients in the metformin plus glyburide combination group, compared to the glyburide alone group, had lower mean FPG concentrations (187±4 vs 261±4 mg/dL; P<0.001), and $HbA_{1c}$ values (7.1±0.1 vs 8.7±0.1%; P<0.001). The effect of metformin alone was similar to that of glyburide alone.<br><br>The changes from baseline were significant compared to glyburide for the following: TC, metformin (P=0.011) and metformin plus glyburide (P=0.001); LDL-C, metformin (P=0.009) and metformin plus glyburide (P=0.001); and TG, each glyburide and metformin plus glyburide (P=0.001)<br><br>Fasting plasma lactate did not change in any of the groups in the course of treatment.<br><br>Secondary:<br>Not reported |
| Chien et al.[81] (2007)<br><br>Glyburide 5 mg BID<br><br>vs<br><br>metformin 500 mg BID<br><br>vs<br><br>glyburide/ metformin 2.5/500mg BID | DB, MC, PG, RCT<br><br>Patients 30 to 75 years of age with type 2 diabetes, BMI 18.5 to 35.0 $kg/m^2$, FPG 140 to 250 mg/dL, and $HbA_{1c}$ 7.0 to 12.0% at the screening visit and FPG ≥140 mg/dL at the second visit, maintained stable sulfonylurea regimen, with or without metformin use | N=100<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, adverse events | Primary:<br>After 16 weeks, the $HbA_{1c}$ increased in patients receiving glyburide (0.52%; P=0.0018) and there was no change in patients receiving metformin (0.09%; P value not significant).<br><br>After 16 weeks, treatment with glyburide/metformin 2.5/500 mg resulted in a greater reduction in $HbA_{1c}$ compared to glyburide or metformin (-1.77%; P<0.001 and -1.34%; P=0.002). Treatment with glyburide/metformin 5/500 mg resulted in a greater reduction in $HbA_{1c}$ compared to glyburide or metformin alone (-1.73%; P<0.001 and -1.30%; P=0.005).<br><br>After 16 weeks, 19 and 24% of patients in the glyburide/metformin groups (2.5/500 mg and 5/500 mg, respectively) had an $HbA_{1c}$ <7.0% compared to 12.0% in the metformin monotherapy group and 6% in the glyburide monotherapy group. |

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| vs<br><br>glyburide/ metformin 5/500 mg BID<br><br>Doses were titrated to a maximum of 4 tablets per day. | | | | Secondary:<br>Mean changes in FPG from baseline were -43 mg/dL in the glyburide group, -41 mg/dL in the metformin group, -98 mg/dL in the glyburide/metformin 2.5/500mg group, and -101 mg/dL in the glyburide/metformin 5/500 mg group. The two glyburide/metformin groups had significant reductions from baseline compared to the monotherapy groups (P<0.0125 compared to glyburide and metformin).<br><br>Treatment with glyburide/metformin 2.5/500 mg resulted in a 55 mg/dL reduction in FPG compared to glyburide (P=0.001) and a 57 mg/dL reduction in FPG compared to metformin (P=0.001). Treatment with glyburide/metformin 5/500 mg resulted in a in a 58 mg/dL reduction in FPG compared to glyburide (P<0.001) and a 60 mg/dL reduction in FPG compared to metformin (P=0.001).<br><br>Ninety-eight episodes of adverse events were reported from the screening visit to the end of the study. Four (14.3%) patients reported adverse events associated with hypoglycemia in the glyburide/metformin 2.5/500 mg group, and two (8.3%) patients reported adverse events associated with gastrointestinal disease among all patients who took metformin during the entire course of the study. The highest incidence of gastrointestinal adverse effects was 32.0% in metformin group, and the lowest was 7.7% in the glyburide/metformin 2.5/500 mg group (P=0.021). |
| Lewin et al.[82] (2007)<br><br>Glyburide 15 mg QD and metformin XR (Glumetza®) 1,500 mg QD, 2,000 mg QD, or 1,000 mg BID<br><br>vs<br><br>glyburide 15 mg QD | DB, MC, RCT<br><br>Type 2 diabetic patients 18 to 79 years of age, drug naïve or previously treated with oral antidiabetic medications (monotherapy with any oral antidiabetic medications up to half the maximum therapeutic dose), | N=607<br><br>30 weeks | Primary:<br>Change baseline $HbA_{1c}$<br><br>Secondary:<br>Changes in $HbA_{1c}$ and FPG at week eight, fructosamine, TC, HDL-C, LDL-C, TG, weight, BMI, discontinuation rates, adverse events | Primary:<br>There were significant reductions in $HbA_{1c}$ from baseline to week 30 in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (-0.74 vs 0.08%, respectively; P<0.001).<br><br>Secondary:<br>There were significant reductions from baseline in mean FPG and in mean $HbA_{1c}$ at week eight in all combined metformin and sulfonylurea groups compared to the sulfonylurea monotherapy group (P<0.001).<br><br>There were significant differences between the combined metformin and sulfonylurea groups and the monotherapy group for mean changes in fructosamine, TC, HDL-C, and LDL-C (P<0.001 for all). |

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| | $HbA_{1c}$ 7.5 to 12.0% in drug-naïve patients or 6.5 to 12.0% in prior drug treatment patients, FPG 200 to 400 mg/dL (drug naïve patients) or 120 to 250 mg/dL (prior drug treatment patients) and C-peptide levels >0.8 ng/mL | | | There were significant increases from baseline in mean weight and BMI in the monotherapy sulfonylurea group (P<0.001). In comparison, there was no significant change in weight and a smaller increase in mean BMI in the combined metformin and sulfonylurea groups (P=0.028).<br><br>There was a significant difference in the rates of hypoglycemia between groups, which were 11.6% in the combined metformin and sulfonylurea groups and 4.2% in the monotherapy sulfonylurea group (P=0.007). However, no significant difference between these two groups was observed for gastrointestinal events.<br><br>Forty patients (9.3%) in the combined metformin and sulfonylurea groups and three patients (2.1%) in the monotherapy sulfonylurea group discontinued treatment due to an adverse event, mainly hypoglycemia (P=0.001). |
| Nauck et al.[83] (2009)<br>LEAD-2<br><br>Liraglutide 0.6, 1.2, and 1.8 mg SC QD<br><br>vs<br><br>placebo<br><br>vs<br><br>glimepiride 4 mg/day<br><br>All patients also received metformin 1,500 to 2,000 mg/day. | AC, DB, DD, MC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age with HbA1c 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m2 | N=1,091<br><br>26 weeks | Primary:<br>Change in baseline HbA1c<br><br>Secondary:<br>Changes in baseline body weight, FPG, seven-point self-monitored glucose concentrations, and β cell function | Primary:<br>HbA1c decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had more efficacious glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in HbA1c between liraglutide and glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride.<br><br>Secondary:<br>Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; P≤0.01).<br><br>Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide |

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| | | | | were similar to glimepiride (-1.3 mmol/L; P value not reported).<br><br>Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; P<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (P values not reported).<br><br>No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (P values not reported).<br><br>Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (P value not reported), and were significantly greater compared to placebo (0.1; P<0.0001).<br><br>Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (P values not reported). |
| Marre et al.[84] (2009)<br>LEAD-1<br><br>Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo<br><br>vs<br><br>placebo plus glimepiride 2 to 4 mg/day | AC, DB, DD, MC, PG, RCT<br><br>Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, $HbA_{1c}$ 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering | N=1,041<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients reaching $HbA_{1c}$ (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP | Primary:<br>After 26 weeks, $HbA_{1c}$ decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in $HbA_{1c}$ were greater in patients previously on an oral glucose lowering agent monotherapy.<br><br>Secondary:<br>The proportion of patients reaching $HbA_{1c}$ targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached $HbA_{1c}$ <7.0 and ≤6.5% compared to 8 and 4% of patients |

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| vs<br><br>placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day | agent combination therapy), and BMI ≤45 kg/m$^2$ | | | receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching $HbA_{1c}$ targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018).<br><br>The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).<br><br>The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported).<br><br>Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported).<br><br>Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR.<br><br>Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported). |
| Chacra et al.[85] (2010) | DB, MC, RCT | N=768 | Primary:<br>Change in baseline | Primary:<br>Saxagliptin significantly decreased $HbA_{1c}$ compared to placebo (-0.54 and |

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| Glyburide 7.5 to 15 mg daily and saxagliptin 2.5 mg QD<br><br>vs<br><br>glyburide 7.5 to 15 mg daily and saxagliptin 5 mg QD<br><br>vs<br><br>glyburide 2.5 to 15 mg daily and placebo | Type 2 diabetics 18 to 77 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.5 to ≤10.0%), on a submaximal sulfonylurea dose for ≥2 months before screening, fasting C-peptide ≥1 ng/mL, and BMI ≤40 kg/m$^2$ | 24 weeks | $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an $HbA_{1c}$ <7.0%, safety | -0.64 vs 0.08%; P<0.0001 for both).<br><br>Secondary:<br>Saxagliptin significantly decreased FPG compared to placebo (2.5 mg; P=0.0218 and 5 mg; P=0.002).<br><br>Saxagliptin significantly decreased PPG $AUC_{0\text{-}3hr}$ compared to placebo (-4,296 and -5,000 vs 1,196 (mg/minute)/(dL); P<0.0001 for both).<br><br>A significantly greater proportion of patients receiving saxagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (22.4 and 22.8 vs 9.1%; P<0.0001 for both).<br><br>Overall saxagliptin was well tolerated. The proportion of patients reporting any adverse event was similar across all treatments; with no evidence of a dose-response relationship. The proportion of patients reporting at least one adverse event and at least one treatment-related adverse event was 75.0 and 19.8, 72.3 and 21.3, and 76.8 and 14.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. No events of Stevens-Johnson syndrome or angioedema were reported. Cardiac disorder events were: 2.0, 4.0 and 3.7% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. Hypertension was reported in 3.6, 6.3, and 2.2% with saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo; however, mean SBP and DBP decreased with all treatments. There was no difference in the incidence of reported and confirmed hypoglycemic events with saxagliptin compared to placebo (P>0.05). Confirmed hypoglycemia occurred in 2.4, 0.8, and 0.7% of patients receiving saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo. |
| Goke et al.[86] (2010)<br><br>Saxagliptin 5 mg/day<br><br>vs<br><br>glipizide 5 mg/day, titrated up to 20 | DB, NI, RCT<br><br>Patients ≥18 years of age with type 2 diabetes with type 2 diabetes, $HbA_{1c}$ >6.5 to 10.0%, and inadequate glycemic control on metformin alone | N=858<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Hypoglycemia, safety | Primary:<br>The per protocol analysis demonstrated non-inferiority of saxagliptin vs glipizide; adulated mean changes from baseline $HbA_{1c}$ were -0.74 vs -0.80%, respectively; the between-group difference was 0.06% (95% CI, -0.05 to 0.16).<br><br>There was a significantly smaller risk in $HbA_{1c}$ (%/week) from week 24 to 52 with saxagliptin vs glipizide (0.001 vs 0.004%; *P*=0.04) indicating a sustained glycemic effect beyond week 24. |

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| mg/day | | | | Secondary:<br>Treatment with saxagliptin vs glipizide was associated with a significantly smaller proportion of patients with hypoglycemic events (3.0 vs 36.3%; *P*<0.0001) and a divergent impact on body weight (adjusted mean change from baseline, -1.1 vs 1.1 kg; *P*<0.0001).<br><br>Excluding hypoglycemic events, the proportion of patients reporting adverse events was smaller with glipizide (60.0 vs 56.7%); however, treatment-related adverse events were less common with saxagliptin (9.8 vs 31.2%), attributable to the higher frequency of hypoglycemia with glipizide. Discontinuation rates resulting from adverse events were similar (approximately 4%). |
| Arechavaleta et al.[87] (2011)<br><br>Sitagliptin 100 mg/day<br><br>vs<br><br>glimepiride 1 mg/day, titrated up to 6 mg/day | DB, NI, RCT<br><br>Patients with type 2 diabetes, $HbA_{1c}$ 6.5 to 9.0%, and on a stable dose of metformin (≥1,500 mg/day) combined with diet and exercise for ≥12 weeks | N=1,035<br><br>30 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary<br>Proportions of patients achieving $HbA_{1c}$ <7.0%, change in baseline FPG, hypoglycemia, body weight | Primary:<br>After 30 weeks, the least squares mean change in $HbA_{1c}$ from baseline was -0.47% with sitagliptin compared to -0.54% with glimepiride, with a between-group difference of 0.07% (95% CI, -0.03 to 0.16). This result met the prespecified criterion for declaring non-inferiority.<br><br>Secondary:<br>The proportions of patients with $HbA_{1c}$ <7.0% at week 30 were 52 and 60% with sitagliptin and glimepiride, respectively.<br><br>The least squares mean change in FPG from baseline was -0.8 mmol/L (95% CI, -1.0 to -0.6) with sitagliptin compared to -1.0 mmol/L (95% CI, -1.2 to -0.8) with glimepiride, for a between-group difference of 0.2 mmol/L (95% CI, -0.1 to 0.4).<br><br>The proportions of patients who reported hypoglycemia were 7 and 22% with sitagliptin and glimepiride (percentage-point difference, -15; P<0.001).<br><br>Relative to baseline, sitagliptin was associated with a mean weight loss compared to a mean weight gain with glimepiride (-0.8 vs 1.2 kg), yielding a between-group difference of -2.0 kg (*P*<0.001). |
| Srivastava et al.[88] (2012) | PG, RCT<br><br>Patients with type 2 | N=50<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>At 18 weeks, both treatments significantly (*P*<0.001) reduced baseline $HbA_{1c}$ (-0.636 vs -1.172%), with 12% of patients receiving sitagliptin and |

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| Sitagliptin 50 mg/day, titrated up to 100 mg/day<br><br>vs<br><br>glimepiride 1 mg/day, titrated up to 2 mg/day | diabetes inadequately controlled with metformin alone | | Secondary:<br>Change in baseline FPG and two-hour PPG, body weight, hypoglycemia | 36% of patients receiving glimepiride achieving target $HbA_{1c}$.<br><br>Secondary:<br>Reductions were significant (*P*<0.001) for both treatments in FPG (-15.49 vs -26.84 mg, respectively) and two-hour PPG (-34.28 vs -44.83 mg, respectively).<br><br>Sitagliptin showed a net decrease in body weight by 0.102 kg, whereas glimepiride showed net increase in body weight by 0.493 kg.<br><br>Incidence of hypoglycemia was 4 and 8% with sitagliptin and glimepiride. |
| Seck et al.[89] (2011)<br><br>Sitagliptin<br><br>vs<br><br>glimepiride | DB, RCT<br><br>Patients with type 2 diabetes receiving metformin | N=803<br><br>1 year | Primary:<br>Composite endpoint of $HbA_{1c}$ reduction, lack of hypoglycemia, and no body weight<br><br>Secondary:<br>Not reported | Primary:<br>Both treatments provided similar degrees of glycemic efficacy (least squares mean difference, -0.67%; between-group difference, -0.01; 95% CI, -0.09 to 0.08); however, significantly more patients receiving sitagliptin achieved an $HbA_{1c}$ reduction >0.5% without hypoglycemia and without an increase in body weight (least squares mean difference, -1.5 vs 1.1 kg; *P*<0.001; between-group difference, -2.5 kg; 95% CI, -3.1 to -2.0).<br><br>Patients receiving glipizide reported more than 10 times as many events of hypoglycemia compared to patients receiving sitagliptin.<br><br>Secondary:<br>Not reported |
| Hermansen et al.[90] (2007)<br><br>Sitagliptin 100 mg QD, glimepiride 4 to 8 mg daily, and metformin 1,500 to 3,000 mg daily<br><br>vs<br><br>sitagliptin 100 mg QD plus | DB, DD, MC, PC, PG, RCT<br><br>Type 2 diabetics 18 to 75 years of age, $HbA_{1c}$ 6.7 to 10.6%, and inadequately controlled on glimepiride with or without metformin | N=441<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, plasma lipids, β cell function, and insulin resistance; safety and tolerability | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ (P<0.001) compared to placebo (treatment difference, -0.74%; 95% CI, -0.90 to -0.57). Patients who were receiving triple therapy (-0.89%; 95% CI, -1.10 to -0.68) had a significantly greater decrease in $HbA_{1c}$ compared to patients receiving combination therapy (-0.57%; 95% CI, -0.82 to -0.32).<br><br>A significantly greater proportion of patients receiving sitagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (17.1 vs 4.8%; P<0.001). A significantly greater proportion of patients receiving triple therapy achieved an $HbA_{1c}$ <7.0% compared to patients receiving combination therapy with glimepiride plus metformin (22.6 vs 1.0%; P<0.001). No difference was observed between combination therapy with |

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| glimepiride 4 to 8 mg daily<br><br>vs<br><br>glimepiride 4 to 8 mg daily, metformin 1,500 to 3,000 mg daily, and placebo<br><br>vs<br><br>glimepiride 4 to 8 mg daily plus placebo | | | | glimepiride plus sitagliptin compared to glimepiride (10.8 vs 8.7%; P<0.638).<br><br>Secondary:<br>Sitagliptin significantly decreased FPG compared to placebo (treatment difference, -20.1 mg/dL; 95% CI, -28.4 to -11.8; P<0.001).<br><br>Sitagliptin demonstrated neutral effects on plasma lipids compared to placebo (specific figures not reported).<br><br>A significant increase in HOMA-B was achieved with sitagliptin compared to placebo (11.3 [95% CI, 4.4 to 18.1] vs -0.7% [95% CI, -8.2 to 6.8]; P<0.001). There were no differences in fasting proinsulin, proinsulin:insulin ratio, HOMA-IR, and QUICKI between the treatments.<br><br>Sitagliptin significantly increased fasting insulin compared to placebo (1.8 vs 0.1 μIU/mL; P<0.001).<br><br>Sitagliptin was well tolerated, both in combination with glimepiride and in triple therapy. There was a higher incidence of overall adverse events (difference of 8.0%; 95% CI, 2.2 to 13.9) observed with sitagliptin compared to placebo, with the majority of that difference due to rates of minor to moderate hypoglycemia.<br><br>A significant increase in body weight of 0.8 kg (95% CI, 0.4 to 1.2) was noted with sitagliptin compared to a slight decrease in weight with placebo (-0.4 kg; 95% CI, -0.8 to 0.1). |
| Nauck et al.[91] (2007)<br><br>Sitagliptin 100 mg QD<br><br>vs<br><br>glipizide 5 to 20 mg QD | AC, DB, MC, NI, PG, RCT<br><br>Patients 18 to 78 years of age with type 2 diabetes who were inadequately controlled ($HbA_{1c}$ ≥6.5 and ≤10%) on metformin | N=1,172<br><br>52 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, fasting insulin, proinsulin, and lipid parameters, β-cell function, insulin | Primary:<br>In both treatments, the least squares mean $HbA_{1c}$ change from baseline was -0.67% (95% CI, -0.75 to -0.59).<br><br>A similar proportion of patients reached an $HbA_{1c}$ level <7.0% in each group (63 vs 59%; difference, 3.9%; 95% CI, -2.8 to 10.7).<br><br>Secondary:<br>The change in FPG was not significantly different between the two treatments. The least squares change from baseline for sitagliptin was - |

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| All patients received metformin ≥1,500 mg daily. | monotherapy | | resistance and sensitivity, safety and tolerability, change in body weight | 0.56 mmol/L (95% CI, -0.81 to -0.30) and -0.42 mmol/L for glipizide (95% CI, -0.67 to -0.17). Sitagliptin led to a decrease in fasting proinsulin compared with an increase with glipizide.<br><br>Patients receiving glipizide demonstrated a higher rate of hypoglycemia as compared to patients receiving sitagliptin (32 vs 5%; P<0.001). No meaningful differences in overall serious clinical adverse events were observed between the two treatments.<br><br>Body weight significantly decreased with sitagliptin; the least squares mean change from baseline was -1.5 kg (95% CI, -2 to -0.9). Body weight significantly increased with glipizide with a least squares mean change from baseline of 1.1 kg (95% CI, 0.5 to 1.6). The between-treatment difference was -2.5 kg (95% CI, -3.1 to -2.0; P<0.001). |
| Schwarz et al.[92] (2008)<br><br>Glyburide 10 mg QD and metformin 2,000 mg QD<br><br>vs<br><br>metformin 2,000 mg QD and nateglinide 120 mg TID before meals | AC, DB, MC, RCT<br><br>Men and women ≥65 years of age with type 2 diabetes, drug naïve, $HbA_{1c}$ 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m$^2$ | N=69<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Change from baseline to week 104 in FPG, two-hour PPG using the incremental area under the curve ($AUC_{0\text{-}120\ min}$) of glucose during oral glucose tolerance tests, the proportion of patients achieving a target $HbA_{1c}$ <7.0 or ≤6.5%, adverse events | Primary:<br>Similar reductions in $HbA_{1c}$ were seen with both treatments. The average change in $HbA_{1c}$ from baseline to week 104 in the nateglinide plus metformin group (–1.2±0.2%) was similar (P=0.310) to that in the glyburide plus metformin group (–1.2±0.1%). The changes in $HbA_{1c}$ were significant for both groups as compared to baseline (P<0.001) after two years of treatment and there was no significant difference between the groups.<br><br>Secondary:<br>Mean change in FPG was –26 ±6 mg/dl in patients receiving nateglinide plus metformin (P<0.001 vs baseline) and –36±6 mg/dL in patients receiving glyburide plus metformin (P<0.001 vs baseline) (P=0.234 between the groups).<br><br>A non-significant reduction in two-hour PPG from baseline was reported in both nateglinide plus metformin and glyburide plus metformin groups (–15±7 mg/dL; P=0.071 and –8±8 mg/dL; P=0.385, respectively).<br><br>The proportion of patients who achieved a target $HbA_{1c}$ <7.0% in the nateglinide plus metformin group was not significantly different compared to the glyburide plus metformin group (70 vs 65%, respectively; P=0.736). |

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| | | | | Similar proportions of patients in the nateglinide plus metformin group and the glyburide plus metformin group maintained a target $HbA_{1c}$ ≤6.5% (40 and 60%, respectively; P=0.206).<br><br>Approximately 94% of patients in the nateglinide plus metformin group and 88% of patients in the glyburide plus metformin group reported one or more adverse events. One mild hypoglycemic event occurred with nateglinide plus metformin treatment vs 8 mild-to-severe hypoglycemic events with glyburide plus metformin treatment (P<0.023). |
| Derosa et al.[93] (2009)<br><br>Glyburide 7.5 to 12.5 mg daily and metformin 1,500 to 3,000 mg daily<br><br>vs<br><br>nateglinide 60 mg TID and metformin 1,500 to 3,000 mg daily | MC, DB, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes mellitus, $HbA_{1c}$ >7.0%), BMI 25 to 28 kg/m$^2$, and hypertensive (SBP/DBP, >130/≥85 mm Hg) | N=248<br><br>12 months | Primary:<br>Changes in BMI, FPG and PPG, $HbA_{1c}$, fasting and postprandial plasma insulin, HOMA index, and lipid profile (TC, LDL-C, HDL-C, TG, apolipoprotein A-I, and apolipoprotein B), SBP, and DBP<br><br>Secondary:<br>Not reported | Primary:<br>BMI did not show any significant change during the study.<br><br>A significant reduction in $HbA_{1c}$ was shown after nine months (P<0.05) and 12 months (P<0.01) in the nateglinide group compared to the baseline value. A significant reduction in $HbA_{1c}$ was seen with glyburide after 12 months (P<0.05) compared to baseline. The $HbA_{1c}$ at 12 months was 6.4% in the nateglinide group compared to 7.3% in the glyburide group (P<0.05).<br><br>After nine and 12 months, mean FPG levels were significantly decreased in the nateglinide and glyburide groups (P<0.05 and P<0.01, respectively) compared to baseline.<br><br>Significant changes in PPG were found at nine months (P<0.05) in the nateglinide group and after 12 months in glyburide and nateglinide groups (P<0.05 and P<0.01, respectively) compared to baseline.<br><br>Fasting plasma insulin and PPI did not show any significant change after three, six, nine and 12 months in both groups compared to the baseline.<br><br>HOMA index decrease was obtained only at 12 months (P<0.05) compared to the baseline value in both groups,<br><br>No significant change was observed in TC, LDL-C, HDL-C, TG, apolipoprotein A-I, apolipoprotein B, SBP, DBP and heart rate in either group after three, six, nine and 12 months. |

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| | | | | Secondary:<br>Not reported |
| Gerich et al.[94] (2003)<br><br>Nateglinide 120 mg TID before meals and metformin 500 to 2,000 mg daily<br><br>vs<br><br>glyburide 1.25 to 10 mg daily and metformin 500 to 2,000 mg daily | DB, MC, RCT (PRESERVE-β Study)<br><br>Men and women 18 to 77 years of age with type 2 diabetes, drug naïve, $HbA_{1c}$ 7.0 to 11.0%, FPG ≤15 mmol/L, BMI 22 to 45 kg/m$^2$ and inadequately controlled on diet and exercise | N=428<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline (average of weeks -2 and 0) to week 104<br><br>Secondary:<br>Change from baseline to week 104 in FPG, and body weight | Primary:<br>Both treatments maintained similar reductions in $HbA_{1c}$. The mean change in $HbA_{1c}$ from baseline to week 104 in the nateglinide plus metformin group (–1.2±0.1%) was similar (P=0.1730) to that in the glyburide plus metformin group (–1.5±0.1%). The changes in $HbA_{1c}$ were significant for both groups as compared to baseline (P<0.0001) after one and two years of treatment and there was no significant difference between the groups.<br><br>Secondary:<br>Mean change in FPG was –1.6±0.2 mmol/L in patients in the nateglinide plus metformin group (P<0.0001 vs baseline) and –2.4±0.2 mmol/L in patients in the glyburide plus metformin group (P<0.0001 vs baseline; P=0.0078 vs nateglinide plus metformin).<br><br>Body weight decreased in the nateglinide plus metformin group (–0.4±0.4 kg) and increased in the glyburide plus metformin group (0.8±0.5 kg). The change from baseline was significant for the glyburide plus metformin group (P=0.0011) only (P=0.8413 for the nateglinide plus metformin group). The difference between groups was statistically significant (P=0.0115). |
| Wolffenbuttel et al.[95] (1999)<br><br>Repaglinide 0.5 to 4 mg TID before each meal<br><br>vs<br><br>glyburide 1.75 to 10.5 mg daily | DB, MC, PG, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes who were being treated with oral blood glucose-lowering agents and/or diet, BMI 21 to 35 kg/m$^2$, and an $HbA_{1c}$ >6.5% when treated with diet only and <12.0% when treated with | N=424<br><br>12 months | Primary:<br>Change in $HbA_{1c}$ and FPG from baseline to the final visit<br><br>Secondary:<br>Change in fasting insulin and lipid levels and four-point blood glucose levels (fasting, before lunch, before supper, and at | Primary:<br>Change in $HbA_{1c}$ levels was not different between groups when compared to baseline. $HbA_{1c}$ levels increased by 0.58% (95% CI, 0.41 to 0.76) in the repaglinide group and by 0.45% (95% CI, 0.22 to 0.69) in the glyburide group.<br><br>In a subset of patients who were treated previously with diet only, $HbA_{1c}$ decreased significantly more during glyburide treatment (–2.4%) vs repaglinide (–1%; P<0.05). The changes in $HbA_{1c}$ in patients who were already being treated with oral agents were similar, 0.6% in the repaglinide group and 0.7% in the glyburide group.<br><br>Changes in fasting plasma glucose from baseline showed a similar trend as the $HbA_{1c}$. |

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| | diet plus oral blood glucose-lowering agents | | bedtime) from baseline to the final visit | Secondary:<br>Mean fasting insulin levels decreased in the repaglinide group (–3 pmol/L) and increased in the glyburide group (+1 pmol/L). There was no treatment difference.<br><br>Changes from baseline in four-point glucose levels were small for both treatment groups.<br><br>Lipid levels (TC, HDL, and TG) did not change during the study. |
| Cesur et al.[96] (2007)<br><br>Repaglinide up to 4 mg QD<br><br>vs<br><br>glimepiride up to 8 mg QD<br><br>vs<br><br>insulin glargine up to 36 U QD | MC, OL, OS, PRO<br><br>Patient 33 to 67 years of age with type 2 diabetes, $HbA_{1c}$ 6.0 to 8.0% taking oral diabetes agents, who were willing to fast throughout Ramadan month | N=65<br><br>Duration not specified | Primary:<br>FBG, PPG, $HbA_{1c}$, fructosamine, BMI, lipid metabolism and hypoglycemia in pre-Ramadan and post-Ramandan fasting<br><br>Secondary:<br>Not reported | Primary:<br>In the fasting group, both FPG and PPG levels showed no significant changes at post-Ramadan and one-month post-Ramadan compared to pre-Ramadan.<br><br>In the nonfasting group, FPG levels did not change significantly throughout the study, whereas PPG levels increased at post-Ramadan (P<0.05 and P<0.01, respectively). At post-Ramadan and one-month post-Ramadan, changes in PPG values in the fasting group were lower compared to the nonfasting group (P<0.01 for both time periods).<br><br>There was no significant change in $HbA_{1c}$ levels between the nonfasting and fasting groups.<br><br>There was a significant increase in fructosamine levels in both fasting group and non-fasting group at one-month post-Ramadan (P<0.01 for both).<br><br>BMI did not change during the study in fasting group but a gradual increase in BMI was seen in the nonfasting group (P<0.05 between pre-Ramadan and post-Ramadan in nonfasting group).<br><br>TC, LDL and TG did not change throughout the study period but HDL levels significantly increased at post-Ramadan in the fasting group (P<0.01). In nonfasting group, LDL and TG levels significantly increased at post-Ramadan (P<0.05 for both).<br><br>At least one hypoglycemia episode was reported in 12.2% of patients in |

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| | | | | the fasting group and 12.5% of patients in the nonfasting group. Hypoglycemia was seen in 14.3% of patients in the glimepiride group, 11.1% in the repaglinide group and 10.0% in the insulin group. There was no significant difference between three drug groups regarding the rate of hypoglycemia.<br><br>Secondary:<br>Not reported |
| Standl et al.[97] (2001)<br><br>Glyburide 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and miglitol 25 mg to 100 mg TID<br><br>vs<br><br>glyburide 3.5 to 5 mg BID to QID, metformin 500 to 850 mg daily, and placebo | DB, MC, PC, PG, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes for at least 3 years, $HbA_{1c}$ ≥7.5 to ≤10.5%, BMI ≤35 kg/m$^2$, stable body weight over the previous 3 months, and inadequately controlled on combination therapy of diet, glibenclamide* and metformin | N=154<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>FPG, PPG, fasting and postprandial serum insulin and TG levels, and urinary glucose | Primary:<br>Addition of miglitol to sulfonylureas and metformin produced a significant reduction in $HbA_{1c}$ (–0.55%; P=0.04) and PPG (–2.6 mmol/L; P=0.0009) from baseline to end point when compared to placebo.<br><br>Secondary:<br>FPG decreased in the miglitol group and was almost unchanged from baseline with placebo, the difference was not significant (P=0.10).<br><br>Fasting insulin levels were unchanged for both groups throughout the study, the difference was not significant (P=0.79).<br><br>Postprandial insulin decreased from baseline to end point, but the difference between the groups was not significant (P=0.26).<br><br>Postprandial TG decreased slightly in the miglitol group and remained unchanged in the placebo group, the difference was not significant (P=0.47). |
| Kabadi et al.[98] (2003)<br><br>Tolazamide 1 gram daily plus premixed 70% NPH and 30% regular insulin daily<br><br>vs | PC, RCT<br><br>Patients with type 2 diabetes mellitus with a lapse of glycemic control, established by documentation of $HbA_{1c}$ >7.4% on ≥2 occasions at an interval of ≥3 | N=40<br><br>7 months | Primary:<br>Changes in body weight, $HbA_{1c}$, and fasting C-peptide concentrations<br><br>Secondary:<br>Changes in daily insulin dose and the number of hypoglycemic | Primary:<br>Changes in body weight were 2.5±0.8 kg for the tolazamide group, 2.6±1.0 kg for the glyburide group, 2.4±0.9 kg for the glipizide XL group, and 2.2±0.7 kg for the glimepiride group, all were significant compared to placebo (P<0.01) after the addition of insulin.<br><br>All groups achieved optimal glycemic control as expressed by $HbA_{1c}$ <7.4%, 1% above the highest normal level of 6.4% in our laboratory as recommended by the American Diabetes Association after the addition of insulin. $HbA_{1c}$ was 6.8±0.4% for tolazamide, 6.9±0.4% for glyburide, 6.7±0.4% for glipizide XL, 6.7±0.3% for glimepiride, and 7.0±0.3% for |

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| glyburide 20 mg daily plus premixed 70% NPH and 30% regular insulin daily<br><br>vs<br><br>glipizide XL plus premixed 70% NPH and 30% regular insulin daily<br><br>vs<br><br>glimepiride 8 mg daily plus premixed 70% NPH and 30% regular insulin daily<br><br>vs<br><br>placebo plus premixed 70% NPH and 30% regular insulin daily | months in each patient while taking oral sulfonylureas consisting of one of these drugs in the maximum recommended daily dose: tolazamide 1 g daily, glyburide 20 mg daily, glipizide XL 20 mg daily, or glimepiride 8 mg daily | | episodes confirmed by finger stick blood glucose <60 mg/ dL | placebo.<br><br>C-peptide levels decreased in all groups. The reduction in the C-peptide level was significantly greater (P<0.05) in the placebo group compared to the sulfonylurea groups. There were no significant differences among the sulfonylurea groups.<br><br>Secondary:<br>Patients receiving sulfonylureas required a significantly lower (P<0.01) daily insulin dose, as well as dose per kilogram of body weight in comparison to patients receiving placebo (P<0.01).<br><br>The daily insulin dose and units per kilogram of body weight was significantly lower (P<0.05) in patients receiving glimepiride in comparison to those receiving tolazamide, glyburide, or glipizide XL.<br><br>The number of hypoglycemic episodes during the last four weeks of the study were significantly lower in the sulfonylurea groups as compared to the placebo group (P<0.01). The differences among the individual sulfonylurea groups were not significantly different. |
| Ligvay et al.[99] (2009)<br><br>Pioglitazone 15 to 45 mg QD plus | RCT, OL<br><br>Patients 21 to 70 years of age with type 2 diabetes who | N=58<br><br>36 months | Primary:<br>$HbA_{1C}$, rate of treatment failures (defined as $HbA_{1c}$ >8.0%), | Primary:<br>After 36 months, $HbA_{1c}$ was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26).<br><br>The percentage of patients achieving $HbA_{1c}$ <7.0% was 100% in both |

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| glyburide 1.25 mg BID<br><br>vs<br><br>insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily<br><br>All patients were receiving metformin 1,000 mg BID<br><br>Doses of medications could be titrated at the investigator's discretion. | were treatment naïve | | hypoglycemia, weight gain, compliance, QOL, and patient satisfaction<br><br>Secondary:<br>Not reported | groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the $HbA_{1c}$ goal at the end of 36 months.<br><br>Three patients in each group reached the "treatment failure" end point.<br><br>The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53).<br><br>In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04).<br><br>Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group.<br><br>There were differences between the groups for any of the 12 QoL domains evaluated.<br><br>All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization.<br><br>Secondary:<br>Not reported |
| Bayraktar et al.[100] (1996)<br><br>Sulfonylurea and acarbose 50 to 100 mg TID<br><br>vs<br><br>sulfonylurea and metformin 500 mg | RCT, XO<br><br>Patients from 30 to 63 years of age with type 2 diabetes for 2 to 20 years, $HbA_{1c}$ >8.5%, FPG >7.7 mmol/L, or a PPG >10 mmol/L on maximum doses of gliclazide† (240 mg | N=18<br><br>20 weeks | Primary:<br>Changes in FBG, PPG, $HbA_{1c}$, TGs, cholesterol, fibrinogen, insulin levels, and C-peptide levels from baseline<br><br>Secondary:<br>Not reported | Primary:<br>Mean FPG, PPG, and $HbA_{1c}$ decreased at the end of each combination treatment period as compared with baseline levels (P<0.05).<br><br>PPG level in the acarbose group was lower than the level achieved by the group using metformin (P<0.05).<br><br>Each saw a statistically significant decrease between pre- and posttreatment two-hour postprandial blood glucose levels (–5.3±0.4 for acarbose vs –2.9±0.3 for metformin; P<0.05). |

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| TID | daily) | | | There were small reductions in fibrinogen, insulin, and C-peptide levels in each group, but the differences were not statistically significant.<br><br>Cholesterol levels remained unchanged with both treatment groups.<br><br>Secondary:<br>Not reported |
| Abbasi et al.[101] (2004)<br><br>Sulfonylurea (existing therapy) and metformin 500 to 1,000 mg BID<br><br>vs<br><br>dietary therapy and metformin 500 to 1,000 mg BID | RCT<br><br>Patients with type 2 diabetes with relatively poor glycemic control with FPG >9.5 mmol/L on dietary therapy alone or sulfonylurea monotherapy, BMI <40 kg/m$^2$, and no apparent cardiovascular disease | N=31<br><br>12 weeks | Primary:<br>Changes in fasting glucose, $HbA_{1c}$, lipid concentrations<br><br>Secondary:<br>Not reported | Primary:<br>FPG decreased to a similar degree with diet therapy (metformin) (12.45±0.48 vs 9.46±0.47 mmol/L; P<0.001) and combined sulfonylurea plus metformin (14.09±0.51 vs 10.57±0.85 mmol/L; P=0.001). The changes in the diet therapy (metformin) group compared to the combined sulfonylurea plus metformin group was not significant (P=0.58).<br><br>Changes in fasting $HbA_{1c}$ from baseline were significant for diet therapy (metformin) (P<0.001) and combined sulfonylurea plus metformin (P<0.002). The changes were not significant when compared to each other (P=0.30).<br><br>Fasting TC, TG, HDL-C, and LDL-C did not change significantly in either treatment group (P=0.64, P=0.34, P=0.48, and P=0.85, respectively) for diet therapy (metformin) compared to combined sulfonylurea plus metformin.<br><br>Fasting remnant lipoprotein cholesterol concentrations were significantly lower in the diet therapy (metformin) group as compared to baseline (0.43±0.09 vs 0.34±0.07 mmol/L; P=0.02). The changes were not significant for diet therapy (metformin) compared to combined sulfonylurea plus metformin (P=0.06).<br><br>Concentrations of FFA and remnant lipoprotein cholesterol concentrations were lower to a similar degree in both groups, whereas day long plasma insulin concentrations were unchanged. Changes in LDL particle diameter and percent of small dense LDL particles between the groups were not significant at end point (P=0.28 and P=0.73, respectively).<br><br>Secondary: |

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| | | | | Not reported |
| Seufert et al.[102] (2008)<br><br>Study 1<br>Gliclazide† 80 to 320 mg daily and metformin (existing therapy)<br><br>vs<br><br>pioglitazone 15 to 45 mg QD and metformin (existing therapy)<br><br>Study 2<br>Sulfonylurea (existing therapy) and pioglitazone 15 to 45 mg QD<br><br>vs<br><br>sulfonylurea (existing therapy) and metformin 850 to 2,550 mg daily | 2 MC, RCT<br><br>Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy ($HbA_{1c}$ 7.5 to 11.0%), and fasting C-peptide >1.5 ng/mL) | N=1,269<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline, FPG, glucose excursions using three-hour oral glucose tolerance test and insulin sensitivity<br><br>Secondary:<br>Not reported | Primary:<br>Study 1<br>The mean change in $HbA_{1c}$ from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20).<br><br>The mean change in FPG from baseline to week 104 was -1.8 mmol/L with pioglitazone and metformin compared to -1.1 mmol/L with gliclazide and metformin (P<0.001).<br><br>Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the 2-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin.<br><br>Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001).<br><br>Study 2<br>The mean change in $HbA_{1c}$ from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173).<br><br>The mean change in FPG from baseline to week 104 was -2.0 mmol/L with pioglitazone and sulfonylurea compared to -1.9 mmol/L with metformin and sulfonylurea (P=0.506).<br><br>The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment.<br><br>Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments). |

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| Matthews et al.[103] (2005)<br><br>Gliclazide† 80 to 320 mg QD and metformin (existing therapy)<br><br>vs<br><br>pioglitazone 15 to 45 mg QD and metformin (existing therapy) | DB, RCT<br><br>Patients with type 2 diabetes that was poorly controlled ($HbA_{1c}$ 7.5 to 11.0%) with metformin monotherapy | N=630<br><br>12 months | Primary:<br>Effect on $HbA_{1c}$<br><br>Secondary:<br>Effect on FPG, insulin, lipoproteins, and C-peptide | Primary:<br>Similar reductions in $HbA_{1c}$ were observed in pioglitazone- (–0.99%) and gliclazide-treated groups (–1.01%; P=0.837).<br><br>Secondary:<br>Similar reductions in FPG were observed in pioglitazone- (–2.1 mmol/L) and gliclazide- (–1.6 mmol/L) treated groups (P=0.506).<br><br>Gliclazide significantly reduced LDL-C compared to pioglitazone (–4.2 vs +10.4 mg/dL; P=0.001).<br><br>Pioglitazone significantly reduced TG (–53.1 vs –19.5 mg/dL; P<0.001) and increased HDL-C (6.9 vs no change; P<0.001) compared to gliclazide. |
| Charbonnel et al.[104] (2005)<br><br>Gliclazide† 80 to 320 mg QD and metformin (existing therapy)<br><br>vs<br><br>pioglitazone 15 to 45 mg QD and metformin (existing therapy) | DB, RCT<br><br>Patients with type 2 diabetes that was poorly controlled ($HbA_{1c}$ 7.5 to 11.0%) with metformin monotherapy | N=630<br><br>24 months | Primary:<br>Effect on $HbA_{1c}$<br><br>Secondary:<br>Effect on FPG, insulin, lipoproteins, and C-peptide | Primary:<br>Similar reductions in $HbA_{1c}$ were observed with pioglitazone add-on therapy (–0.89%) and with gliclazide add-on therapy (–0.77%; P=0.200) after 2 years.<br><br>Secondary:<br>Significant reductions in FPG were observed with pioglitazone add-on therapy (–1.8 mmol/L) compared to gliclazide add-on therapy (–1.1 mmol/L; P<0.001) after two years.<br><br>Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (–6 vs +2 mg/dL; P<0.001).<br><br>Pioglitazone add-on therapy significantly reduced TG (–23 vs –7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy.<br><br>No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported.<br><br>Less weight gain was observed with gliclazide add-on therapy to |

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| | | | | metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg). |
| Hanefeld et al.[105] (2004)<br><br>Sulfonylurea (existing therapy) and pioglitazone 15 to 45 mg QD<br><br>vs<br><br>sulfonylurea (existing therapy) and metformin 850 to 2,250 mg | DB, MC, PG, RCT<br><br>Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy | N=639<br><br>12 months | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio) | Primary:<br>$HbA_{1c}$ was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments).<br><br>Secondary:<br>FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant.<br><br>Pioglitazone addition to sulfonylurea significantly reduced TG (–16 vs –9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition.<br><br>LD-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001).<br><br>Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017).<br><br>Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group. |
| Comaschi et al.[106] (2008)<br><br>Metformin/ glibenclamide* fixed dose combination 400/2.5 mg 1 to 3 tablets daily<br><br>vs<br><br>Pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic | MC, OL, PG, RCT<br><br>Patients aged ≥35 years with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, $HbA_{1c}$ 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L | N=250<br><br>6 months | Primary:<br>Change in $HbA_{1c}$ from baseline to six months<br><br>Secondary:<br>Change in lipid profiles after six months of treatment | Primary:<br>Pioglitazone-based and fixed-dose metformin/glibenclamide resulted in similar reductions in $HbA_{1c}$ (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370).<br><br>Secondary:<br>No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479).<br><br>The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001).<br><br>There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination |

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| therapy (either metformin or sulfonylurea) | | | | of metformin/glibenclamide (-0.01 mmol/L; P=0.677).<br><br>There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425)<br><br>There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045). |
| Home et al.[107] (2007)<br><br>Sulfonylurea plus metformin<br><br>vs<br><br>rosiglitazone plus either metformin or a sulfonylurea | MC, OL, RCT<br><br>Patients with type 2 diabetes between 40 and 75 years of age, BMI >25.0 kg/m$^2$, $HbA_{1c}$ 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled | N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103 rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea)<br><br>Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be 6 years) | Primary:<br>Hospitalization or death from cardiovascular causes<br><br>Secondary:<br>Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke | Primary:<br>For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication.<br><br>Secondary:<br>There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI.<br><br>Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006). |

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| | hypertension | | | |
| Home et al.[108] (2009)<br><br>Sulfonylurea plus metformin<br><br>vs<br><br>rosiglitazone plus either metformin or a sulfonylurea | MC, OL, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | N=4,458<br><br>5.5 years (mean follow-up) | Primary:<br>Time to first cardiovascular hospitalization or cardiovascular death<br><br>Secondary:<br>Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke | Primary:<br>The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93).<br><br>Secondary:<br>There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95%, CI 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50).<br><br>Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010).<br><br>There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures. |
| Home et al.[109] (2007)<br><br>Sulfonylurea plus metformin<br><br>vs<br><br>rosiglitazone plus | MC, OL, PG, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea | N=1,122<br><br>18 months | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell | Primary:<br>At 18 months, $HbA_{1c}$ reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant).<br><br>Secondary:<br>Differences in FPG were not significant at 18 months (rosiglitazone vs |

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| either metformin or a sulfonylurea | monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | | function (HOMA %β), body weight, inflammatory/ thrombotic markers, CRP | sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089).<br><br>Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for both).<br><br>HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant).<br><br>Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003).<br><br>At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant).<br><br>There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001). |
| Komajda et al.[110] (2008)<br><br>Sulfonylurea plus metformin<br><br>vs<br><br>rosiglitazone plus either metformin | RCT, MC, OL, (RECORD)<br><br>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea | N=668<br><br>12 months | Primary:<br>Change from baseline in 24-hour ambulatory BP at six months and 12 months<br><br>Secondary:<br>Not reported | Primary:<br>For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031).<br><br>Reductions in 24-hour DBP were greater at six months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| or a sulfonylurea | monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | | | At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016).<br><br>At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mm Hg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003).<br><br>At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P=not significant; DBP; P=0.049).<br><br>Secondary:<br>Not reported |
| Hamann et al.[111] (2008)<br><br>Glibenclamide* 5 mg or gliclazide† 80 mg and metformin 2,000 mg daily (SU+MET)<br><br>vs<br><br>rosiglitazone/ metformin FDC 4 mg/2,000 mg daily (RSG+MET) | RCT, DB, PG<br><br>Overweight patients (BMI ≥25 kg/m$^2$) with type 2 diabetes, $HbA_{1c}$ 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks | N=596<br><br>52 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to week 52<br><br>Secondary:<br>Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP | Primary:<br>At week 52, mean change in $HbA_{1c}$ from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25).<br><br>Secondary:<br>Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095).<br><br>The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 $HbA_{1c}$%/year, respectively; P=0.0002).<br><br>Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001).<br><br>Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001).<br><br>After 52 weeks, 24-hour diastolic and systolic ambulatory BP were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BP (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Duckworth et al.[112] (2003)<br><br>Glyburide/ metformin | RETRO<br><br>Patients 18 to 80 years of age with type 2 diabetes were eligible if they had received a combination product with glyburide and metformin for ≥90 days and had been treated with glipizide or glyburide plus metformin for ≥6 months prior to switching to the combination product of glyburide/ metformin | N=72<br><br>196 days (mean follow-up) | Primary:<br>Changes in $HbA_{1c}$, lipid parameters, weight<br><br>Secondary:<br>Not reported | Primary:<br>The mean baseline $HbA_{1c}$ in the total population was 8.3±1.7%. The mean reduction in $HbA_{1c}$ was 0.6% (P=0.002) with a mean follow-up of 196 days after the initiation of glyburide/metformin. The mean daily doses of glyburide and metformin at baseline and at final follow-up were 17.2 and 1,607 mg and 14.7 and 1,750 mg, respectively.<br><br>The greatest decrease in $HbA_{1c}$ was observed in patients with a baseline $HbA_{1c}$ ≥8.0% (n=37). This group had a mean reduction of $HbA_{1c}$ of 1.3% (P=0.0002) with similar doses of glyburide (14.7 vs 16.9 mg; P=0.077) and metformin (1,743 vs 1,624 mg; P=0.11) in both treatment periods.<br><br>There were no significant changes in TC, HDL-C, LDL-C, or TG from baseline.<br><br>There were no significant changes in body weight from a baseline level of 104.3 kg to the last follow-up weight of 104.0 kg (P=0.0645).<br><br>There were no significant differences in patient adherence to the regimen (92.4% before vs 90.9% after).<br><br>Secondary:<br>Not reported |
| Blonde et al.[113] (2003)<br><br>Glyburide coadministered with metformin<br><br>vs<br><br>glyburide/ metformin | RETRO<br><br>Patients with type 2 diabetes new to the combination product glyburide/ metformin or glyburide coadministered with metformin between August 2000 and July 2001 and had $HbA_{1c}$ levels at baseline within 79 | N=1,421<br><br>~ 6 month (follow-up period) | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Not reported | Primary:<br>The mean $HbA_{1c}$ for the two groups at baseline were similar, 9.1% for the combination product and 9.2% for the individual agents coadministered. During the follow-up period, patients taking the combination product had a lower mean daily dose of glyburide and metformin than patients receiving the individual agents coadministered regardless of baseline $HbA_{1c}$.<br><br>Fifty-six percent of patients in the combination group achieved an $HbA_{1c}$ <7.0% compared to 31.2% of patients receiving the individual agents coadministered. The mean $HbA_{1c}$ decrease from baseline in the combination group was -2.02% and -1.49% when the individual agents were coadministered. The regression results indicated that patients taking the combination product had a significantly greater (P<0.0001) reduction |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | to 194 days of initiating combination therapy | | | in $HbA_{1c}$ than patients receiving the individual agents coadministered.<br><br>Patients receiving the combination product with baseline $HbA_{1c}$ ≥8.0% experienced a significantly (P<0.0001) greater decrease in $HbA_{1c}$ of 2.93% compared to 1.92% for the individual agents coadministered.<br><br>For patients with baseline $HbA_{1c}$ <8.0%, the difference between the $HbA_{1c}$ responses remained significant. The reductions in $HbA_{1c}$ were smaller for both the combination product and the individual agents coadministered (-0.54 and -0.23%; P=0.0017).<br><br>Patients were more adherent with the combination product than the individual agents coadministered (84% days with drug supply vs 76% days with drug supply, respectively; P<0.0001). The mean decreases in $HbA_{1c}$ were similar for those patients ≥80% adherent and <80% adherent for the combination product (2.12 vs 2.19%; P value not significant) and the individual agents coadministered (1.47 vs 1.24%; P value not significant).<br><br>Secondary:<br>Not reported |
| Johnson et al.[114] (2005)<br><br>Sulfonylurea monotherapy<br><br>vs<br><br>metformin monotherapy<br><br>vs<br><br>combination therapy of sulfonylureas and | RETRO<br><br>Patients ≥30 years of age who were new users of oral antidiabetic drugs (sulfonylurea monotherapy, metformin monotherapy, or combination therapy of sulfonylureas and metformin) | N=4,124<br><br>N=2,138 sulfonylurea monotherapy<br><br>N=923 metformin monotherapy<br><br>N=1,081 combination therapy<br><br>Duration not reported | Primary:<br>Composite end point of fatal or nonfatal cardiovascular related events<br><br>Secondary:<br>Not reported | Primary:<br>A total of 381 patients died from cardiovascular causes and 715 were hospitalized at least once for cardiovascular reasons. Patients in the metformin monotherapy group had the lowest nonfatal hospitalization rate for cardiovascular causes (53.7 hospitalizations per 1,000 person years) compared to sulfonylurea monotherapy patients (75.3 per 1,000 person years; P<0.05) and compared to combination therapy patients (90.2 per 1,000 person years; P<0.05). Nonfatal cardiovascular related hospitalization rates were similar for sulfonylurea monotherapy patients and combination therapy patients (P=0.08).<br><br>Metformin monotherapy was associated with a lower risk of the composite end point (adjusted HR, 0.81; 95% CI, 0.68 to 0.97) as compared to sulfonylurea monotherapy.<br><br>Cardiovascular hospitalizations were similar for sulfonylurea monotherapy |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| metformin | | | | and combination therapy (P=0.32).<br><br>Secondary:<br>Not reported |
| Swinnen et al.[115] (2010)<br><br>Continuation of secretagogues (sulfonylureas or meglitinides)<br><br>vs<br><br>discontinuation of secretagogues (sulfonylureas or meglitinides)<br><br>All patients received existing metformin regimens and initiated insulin therapy. | PRO<br><br>Patients 40 to 75 years of age with type 2 diabetes, $HbA_{1c}$ 7.0 to 10.5% receiving oral glucose-lowering drugs | N=865<br><br>24 weeks | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary:<br>Hypoglycemia, body weight, insulin dose | Primary:<br>In patients continuing secretagogue treatment, $HbA_{1c}$ decreased to 7.0±0.8% at week 12 compared to 7.4±0.9% in patients discontinuing their secretagogues. Endpoint $HbA_{1c}$ level was 7.2±0.9% in both treatment groups. The difference in mean $HbA_{1c}$ reduction during the trial was not significant (-1.59±1.08% for patients continuing secretagogues and -1.30±1.14% for patients discontinuing secretagogues; P=0.382).<br><br>Secondary:<br>Compared to patients who discontinued secretagogues, patients who continued secretagogues experienced significantly more hypoglycemia (40.0 vs 24.5%; P<0.001) and gained significantly more weight (1.44±3.04 vs 0.43±3.00 kg; P<0.001).<br><br>End of trial insulin doses, were significantly lower in patients who continued secretagogues compared to patients who discontinued secretagogues (P<0.001). |
| **Gestational Diabetes** | | | | |
| Moore et al.[116] (2010)<br><br>Glyburide 2.5 to 10 mg BID<br><br>vs<br><br>metformin 500 to 2,000 mg daily (divided doses) | DB, PG, RCT<br><br>Women with gestational diabetes between 11 and 33 weeks gestation at the time of randomization | N=149<br><br>Variable duration | Primary:<br>Glycemic control<br><br>Secondary:<br>Medication failure rate, macrosomia, admission to the neonatal intensive care unit, five-minute Apgar score <7, | Primary:<br>There was no difference between the glyburide or metformin groups in mean fasting (P=0.23) or two-hour PPG concentrations (post-breakfast, P=0.15; post-lunch, P=0.28; post-dinner, P=0.32).<br><br>Secondary:<br>Twenty-six patients (34.7%) in the metformin group and 12 patients (16.2%) in the glyburide group did not meet glycemic goals and required insulin therapy (P=0.01). The failure rate of metformin was 2.1 times higher than the failure rate of glyburide (95% CI, 1.2 to 3.9; OR, 2.7). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Insulin was started in treatment failures and oral medication was discontinued. | | | birth trauma, preeclampsia, maternal and neonatal hypoglycemia, and route of delivery | Macrosomia occurred in 5.4% of patients in the glyburide group and 1.3% of patients in the metformin group (P=0.20). The mean birth weight of babies in the metformin group was smaller than the mean birth weight of babies in the glyburide group (P=0.02). Other neonatal outcomes did not differ between the two groups.<br><br>There were four neonatal intensive care unit admissions in the metformin group and one neonatal intensive care unit admission in the glyburide group (P=0.37). There were no five-minute Apgar scores <7 in either group. There was one shoulder dystocia in the glyburide group and one third-degree tear in the metformin group (P=0.49).<br><br>The incidence of maternal hypoglycemia and preeclampsia was not different between the two treatment groups (P=0.56 and P>0.50, respectively). One infant in the metformin group experienced hypoglycemia with blood glucose less than 40 mg/dL.<br><br>Excluding elective repeat cesarean deliveries, there were 11 cesarean deliveries in the metformin group compared with two cesarean deliveries in the glyburide group (P=0.02). |

*Synonym for glyburide.
†Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily, XL=extended-release, XR=extended-release
Study abbreviations: AC=active-comparator, DB=double-blind, DD=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: AUC=area under the curve, BMI=body mass index, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4=dipeptidyl peptidase-4, EQ-5D=EuroQol questionnaire, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide-1, $HbA_{1c}$= glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta cell function, HOMA-IR=homeostasis model assessment-estimated insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, ITT=intention-to-treat, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PPAR=peroxisome proliferator-activated receptors, PPG=postprandial plasma glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, TZD=thiazolidinedione, WMD=weighted mean difference

**Additional Evidence**

Dose Simplification
Dezii et al. evaluated the differences in adherence and persistence with a once-daily extended-release formulation of glipizide gastrointestinal therapeutic system (GITS) and a twice-daily immediate-release formulation of glipizide. After one year of treatment, adherence rates were 60.5% in the once-daily group compared to 52.0% in the twice-daily group (P=0.027). Persistence rates were 44.4% in the once-daily group and 35.8% in the twice-daily group (P=0.016).[117] Donnan et al. evaluated the patterns and predictors of adherence in patients with type 2 diabetes receiving treatment with a single antidiabetic agent. Adherence was ≥90% in 31.3% of the patients prescribed sulfonylureas and 33.9% of patients prescribed metformin. Patients with better adherence tended to be younger and had a shorter duration of diabetes. There were linear trends of poorer adherence with each increase in the daily number of tablets taken for both sulfonylurea (P=0.001) and metformin (P=0.074) indices. There were significant trends of decreasing adherence with the number of concomitant medications for the sulfonylurea group (P=0.0001) and metformin group (P=0.007).[118]

Several retrospective database analyses have been conducted to assess adherence rates with various antidiabetic agents. Blonde et al. evaluated adherence rates in patients beginning treatment with a sulfonylurea and metformin. The first group consisted of patients who were receiving glyburide/metformin as a fixed-dose combination. The second group consisted of patients who were receiving the combination of glyburide and metformin as separate formulations. The investigators found that patients were more adherent with the fixed-dose combination product than with the agents administered in separate formulations (84% days with drug supply vs 76% days with drug supply, respectively, P<0.0001).[113] Duckworth et al. evaluated patients who were taking glipizide or glyburide in combination with metformin (administered as separate formulations) for at least 6 months. Patients were then switched to a fixed-dose combination of glyburide/metformin. The investigators found no significant difference in adherence (92.4% before vs 90.9% after the switch).[112] Melikian et al. evaluated adherence rates in newly treated or previously treated patients with type 2 diabetes. The investigators found no difference in adherence rates during the initial 6 months of therapy among patients who were receiving metformin monotherapy, glyburide monotherapy, or metformin and glyburide combination therapy (administered as separate formulations) as compared to patients who received a fixed-dose combination of glyburide/metformin. Significantly lower adherence rates were seen in patients receiving metformin monotherapy and glyburide monotherapy who had a second agent added at their regimen (54%; 95% CI, 0.52 to 0.55) compared to patients who were switched to a fixed-dose combination of glyburide/metformin (77%; 95% CI, 0.72 to 0.85).[119]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |

| Relative Cost Index Scale | |
|---|---|
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 10. Relative Cost of the Sulfonylureas**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| **Single Entity Agents** | | | | |
| Chlorpropamide | tablet | N/A | N/A | $ |
| Glimepiride | tablet | Amaryl®* | $$$$ | $ |
| Glipizide | extended-release tablet, tablet | Glucotrol®*, Glucotrol XL®* | $-$$ | $ |
| Glyburide | tablet | DiaBeta®* | $-$$$$ | $ |
| Glyburide, micronized | tablet | Glynase®* | $-$$$$ | $ |
| Tolazamide | tablet | N/A | N/A | $$-$$$$ |
| Tolbutamide | tablet | N/A | N/A | $$$$ |
| **Combination Products** | | | | |
| Glipizide and metformin* | tablet | N/A | N/A | $$ |
| Glyburide, micronized and metformin | tablet | Glucovance®* | $$$$ | $ |

*Generic is available in at least one dosage form or strength.
N/A=Not available

## X. Conclusions

The sulfonylureas are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-10] All of the sulfonylureas are available in a generic formulation, including the fixed-dose combination products.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with a high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The sulfonylureas are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note that sulfonylureas are associated with weight gain and a greater risk of inducing hypoglycemia compared to other available antidiabetic medications. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/meglitinide, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one sulfonylurea over another is not stated.[13-22]

The sulfonylureas have been evaluated in numerous clinical trials.[25-119] In monotherapy studies, glipizide and glyburide were found to be equally efficacious, regardless of the dosage form used.[32-34,35,37,40] Several studies evaluated the efficacy of sulfonylureas in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[73-75,77-81,85] However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.[92,102-106,109,111]

There is insufficient evidence to support that one brand sulfonylurea is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Thiazolidinediones
# AHFS Class 682028
# November 14, 2012

## I. Overview

The antidiabetic agents are categorized into nine different American Hospital Formulary Service classes, including alpha-glucosidase inhibitors, amylinomimetics, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, incretin mimetics, insulins, meglitinides, sulfonylureas and thiazolidinediones. The agents which make up these classes differ with regards to their mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-6] They are selective agonists of the peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action. When activated, PPARγ regulates the transcription of insulin-responsive genes responsible for glucose production, transportation and utilization. PPARγ also plays a role in the regulation of fatty acid metabolism. The thiazolidinediones increase the insulin sensitivity of adipose tissue, skeletal muscle and the liver. This results in increased glucose uptake and metabolism, suppression of hepatic glucose production, and decreased plasma free fatty acid concentrations.[1-8]

Both pioglitazone and rosiglitazone are available in combination with either metformin or glimepiride. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[4,6] Glimepiride improves glycemic control by stimulating the release of insulin from pancreatic beta cells.[3,5]

The thiazolidinediones that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available; however, metformin and glimepiride are available generically in a separate formulation. This class was last reviewed in May 2010.

**Table 1. Thiazolidinediones Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Pioglitazone | tablet | Actos®* | Actos® |
| Rosiglitazone | tablet | Avandia® | none |
| **Combination Products** | | | |
| Pioglitazone and glimepiride | tablet | Duetact® | none |
| Pioglitazone and metformin | tablet | Actoplus Met®*, Actoplus Met XR® | pioglitazone and metformin |
| Rosiglitazone and glimepiride | tablet | Avandaryl® | none |
| Rosiglitazone and metformin | tablet | Avandamet® | none |

*Generic available in at least one dosage form and/or strength.
PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current clinical guidelines are summarized in Table 2. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

**Table 2. Treatment Guidelines Using the Thiazolidinediones**

| Clinical Guideline | Recommendation(s) |
|---|---|
| American Diabetes Association (ADA): **Standards of Medical Care in** | Current criteria for the diagnosis of diabetes<br>• The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin ($HbA_{1c}$) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 |

| Clinical Guideline | Recommendation(s) |
|---|---|
| **Diabetes[9] (2012)** | mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL).<br><br>Prevention/delay of type 2 diabetes<br>• An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.4%.<br>• Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an $HbA_{1c}$ 5.7 to 6.7%, especially for those with a body mass index >35 kg/m$^2$, age <60 years, and women with prior gestational diabetes mellitus.<br><br>Glycemic goals in adults<br>• Lowering $HbA_{1c}$ to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable $HbA_{1c}$ goal for many nonpregnant adults is <7.0%.<br>• It may be reasonable for providers to suggest more stringent $HbA_{1c}$ goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.<br>• Conversely, less stringent $HbA_{1c}$ goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.<br><br>Pharmacologic and overall approaches to treatment-type 2 diabetes<br>• At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated.<br>• In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or $HbA_{1c}$, consider insulin therapy, with or without additional agents, from the onset.<br>• If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the $HbA_{1c}$ target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. |
| American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[10] (2012)** | Key points<br>• Glycemic targets and glucose-lowering therapies must be individualized.<br>• Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.<br>• Unless there are prevalent contraindications, metformin is the optimal first line drug.<br>• After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.<br>• All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.<br>• Comprehensive cardiovascular risk reduction must be a major focus of therapy.<br><br>Initial drug therapy<br>• It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent.<br>• Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, $HbA_{1c}$ goals.<br>• Patients with high baseline $HbA_{1c}$ (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance.<br>• If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or $HbA_{1c}$ (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.<br>• If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.<br>• Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.<br>• Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.<br><br>Advancing to dual combination therapy<br>• If monotherapy alone does not achieve/maintain $HbA_{1c}$ target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the $HbA_{1c}$, the more likely insulin will be required.<br>• On average, any second agent is typically associated with an approximate further reduction in $HbA_{1c}$ of approximately 1.0%.<br>• If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.<br>• Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.<br>• It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.<br>• For all medications, consideration should also be given to overall tolerability.<br><br>Advancing to triple combination therapy |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.<br>• Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., $HbA_{1c}$ ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.<br>• In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.<br>• Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence. |
| American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus[11] (2012)** | • Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.<br>• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. |

**Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations**

| **Initial Drug Monotherapy** | Metformin |
|---|---|
| Efficacy (↓$HbA_{1c}$) | High |
| Hypoglycemia | Low risk |
| Weight | Neutral/loss |
| Side Effects | Gastrointestinal/lactic acidosis |

If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)

| **Two Drug Combin-ations** | Metformin + sulfonyl-urea | Metformin + thia-zolidinedione (TZD) | Metformin + DPP-4 inhibitor | Metformin + GLP-1 receptor agonist | Metformin + insulin (usually basal) |
|---|---|---|---|---|---|
| Efficacy (↓$HbA_{1c}$) | High | High | Inter-mediate | High | Highest |
| Hypo-glycemia | Moderate risk | Low risk | Low risk | Low risk | High risk |
| Weight | Gain | Gain | Neutral | Loss | Gain |
| Major Side Effects | Hypo-glycemia | Oedema, heart failure, bone fracture | Rare | Gastro-intestinal | Hypo-glycemia |

If needed to reach individualized $HbA_{1c}$ target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)

| **Three Drug Combin-ations** | Metformin + sulfonyl-urea + | Metformin + TZD + | Metformin + DPP-4 inhibitor + | Metformin + GLP-1 receptor agonist + | Metformin + insulin therapy + |
|---|---|---|---|---|---|
| | TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin | Sulfonyl-urea, TZD, or insulin | Sulfonyl-urea, TZD, or insulin | TZD, DPP-4 inhibitor, or GLP-1 receptor agonist |

If combination therapy that includes basal insulin has failed to achieve $HbA_{1c}$ target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents

| **More Complex Insulin Strategies** | Insulin (multiple daily doses) |
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| Clinical Guideline | Recommendation(s) |
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| | • It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia. |
| American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan[12] (2011)** | Antihyperglycemic pharmacotherapy<br>• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Algorithm for Glycemic Control.[13]<br>• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.<br>• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.<br>• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.<br>• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.<br>• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.<br>• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia.<br>• When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia.<br>• Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, $HbA_{1c}$, and weight.<br>• Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.<br>• Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained.<br>• Most patients with an initial $HbA_{1c}$ level >7.5% will require combination therapy using agents with complementary mechanisms of action. |
| American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) | Principles underlying the algorithm<br>• Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes.<br>• Achieving an $HbA_{1c}$ 6.5% is recommended as the primary goal; |

| Clinical Guideline | Recommendation(s) |
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| Consensus Panel on Type 2 Diabetes Mellitus:<br>**Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control[13] (2009)** | however, the goal must be customized for individual patients.<br>• If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised.<br>• When using combination therapy it is important to have medications that have complementary mechanisms of action.<br>• Effectiveness of therapy must be re-evaluated frequently, typically every two to three months.<br><br><u>Stratification by current $HbA_{1c}$</u><br>• Patients with an $HbA_{1c}$ ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved.<br>• Patients with an $HbA_{1c}$ 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered.<br>• Patients with an $HbA_{1c}$ >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated.<br><br><u>Management of patients with a $HbA_{1c}$ 6.5 to 7.5%</u><br>• In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy.<br>• If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options.<br>• Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor, or a secretagogue (glinide or sulfonylurea).<br>• The GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues.<br>• Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 receptor agonists are preferred due to its greater effectiveness in reducing PPG excursions (relative to the DPP-4 inhibitors) and the potential for weight loss.<br>• Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a lower risk of hypoglycemia and greater flexibility in timing of administration. |

| Clinical Guideline | Recommendation(s) |
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| | • The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles.<br>• If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD.<br>  o Metformin + GLP-1 receptor agonist + glinide.<br>  o Metformin + GLP-1 receptor agonist + sulfonylurea.<br>  o Metformin + DPP-4 inhibitor + TZD.<br>  o Metformin + DPP-4 inhibitor + glinide.<br>  o Metformin + DPP-4 inhibitor + sulfonylurea.<br>• Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy.<br>• The GLP-1 receptor agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying.<br>• The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia.<br>• The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.<br>• When triple therapy fails to achieve glycemic goals, insulin therapy is needed.<br><br><u>Management of patients with a $HbA_{1c}$ 7.6 to 9.0%</u><br>• The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients.<br>• The following combination therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist.<br>  o Metformin + DPP-4 inhibitor.<br>  o Metformin + TZD.<br>  o Metformin + sulfonylurea.<br>  o Metformin + glinide.<br>• Metformin is again considered the cornerstone of combination therapy.<br>• A GLP-1 receptor agonist or DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 receptor agonist is given higher priority in view of its somewhat greater effect on reducing PPG excursions and its potential for inducing substantial weight loss.<br>• TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure, and fractures associated with their use.<br>• Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia.<br>• When combination therapy fails to achieve glycemic goals, triple therapy should be started.<br>• The following triple therapy regimens are considered:<br>  o Metformin + GLP-1 receptor agonist + TZD. |

| Clinical Guideline | Recommendation(s) |
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| | ○ Metformin + DPP-4 inhibitor + TZD.<br>○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>○ Metformin + TZD + sulfonylurea.<br>• Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 receptor agonist or a DPP-4 inhibitor.<br>• The preference for metformin and the GLP-1 receptor agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia.<br>• TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia.<br>• A GLP-1 receptor agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing PPG excursions and the possibility that it might induce considerable weight loss.<br>• Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia.<br>• α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited $HbA_{1c}$-lowering potential.<br>• The considerations for insulin therapy in these patients are similar to those used in patients with an $HbA_{1c}$ 6.5 to 7.5%.<br><br><u>Management of patients with a $HbA_{1c}$ >9.0%</u><br>• Patients who are drug-naïve with an $HbA_{1c}$ >9.0% are unlikely to achieve glycemic goals with the use of one, two, or even three agents (other than insulin).<br>• For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient.<br>• The following combination and triple therapy regimens are considered:<br>○ Metformin + GLP-1 receptor agonist.<br>○ Metformin + GLP-1 receptor agonist + sulfonylurea.<br>○ Metformin + DPP-4 inhibitor.<br>○ Metformin + DPP-4 inhibitor + sulfonylurea.<br>○ Metformin + TZD.<br>○ Metformin + TZD + sulfonylurea.<br>○ Metformin + GLP-1 receptor agonist + TZD.<br>○ Metformin + DPP-4 inhibitor + TZD.<br>• Metformin again provides the foundation of treatment in these patients.<br>• An incretin-based therapy can be added with a GLP-1 receptor agonist being preferred due to its greater effectiveness at controlling post-prandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this $HbA_{1c}$ range.<br>• A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action.<br>• If patients are symptomatic (polydipsia, polyuria, weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay.<br>• Insulin therapy for these patients follows the same principals as |

| Clinical Guideline | Recommendation(s) |
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| | outlined previously for patients with different $HbA_{1c}$ levels.<br>• This algorithm favors the use of GLP-1 receptor agonists (at the time of publication only exenatide had Food and Drug Administration approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues.<br>• The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period.<br>• A TZD is considered a "well-validated" effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects.<br>• The three classes of medications; α-glucosidase inhibitors, colesevelam, and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| American Association of Clinical Endocrinologists (AACE):<br>**Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus[14] (2007)** | <u>Glycemic management-all patients with diabetes</u><br>• Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following:<br>  ○ $HbA_{1c} \leq 6.5\%$.<br>  ○ FPG <100 mg/dL.<br>  ○ Two-hour PPG <140 mg/dL.<br>  ○ Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy.<br>  ○ Initiate self-monitoring blood glucose levels.<br><br><u>Glycemic management-patients with type 2 diabetes</u><br>• Aggressively implement all appropriate components of care at the time of diagnosis.<br>• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved.<br>• First assess current $HbA_{1c}$ level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns.<br>• After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved.<br>• Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication.<br>• Consider insulin therapy in patients with $HbA_{1c}$ >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of $HbA_{1c}$ levels.<br>• Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when $HbA_{1c}$ >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. |

| Clinical Guideline | Recommendation(s) |
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| | • Consider a continuous SC insulin infusion in insulin-treated patients.<br>• Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy.<br>• Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump.<br>• Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.<br>• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily.<br>• Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels.<br>• Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia.<br>• Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.<br>• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL.<br><br><u>Clinical support-clinical considerations in patients with type 2 diabetes</u><br>• Combining therapeutic agents with different modes of action may be advantageous.<br>• Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.<br>• Insulin is the therapy of choice in patients with advanced chronic kidney disease.<br>• Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline.<br>• The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin.<br>• Carefully assess PPG levels if the $HbA_{1c}$ level is elevated and pre-prandial glucose measurements are at target levels.<br>• Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the $HbA_{1c}$ level is at or near target.<br>• Individualize treatment regimens to accommodate patient exercise patterns.<br>• Administer basal insulin in the evening if fasting glucose is elevated.<br>• Long-acting insulin analogs are associated with less hypoglycemia |

| Clinical Guideline | Recommendation(s) |
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| | than NPH insulin. |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[15] (2009)** | DPP-4 inhibitors<br>• Consider adding a DPP-4 inhibitor to metformin (as second-line therapy) instead of a sulfonylurea when blood glucose control is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a DPP-4 inhibitor to sulfonylurea (as second-line therapy) when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or if metformin is contraindicated.<br>• Consider adding a DPP-4 inhibitor as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• A DPP-4 inhibitor may be preferable to a thiazolidinedione if:<br>  o Further weight gain would cause or exacerbate significant problems associated with a high body weight.<br>  o A thiazolidinedione is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a thiazolidinedione.<br>• There may be some individuals for whom either a DPP-4 inhibitor or a TZD may be suitable. The choice of treatment should be based on patient preference.<br><br>TZDs<br>• Consider adding a TZD instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.<br>• Consider adding a TZD as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate ($HbA_{1c}$ ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.<br>• Consider adding a TZD as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and insulin is unacceptable or inappropriate.<br>• Only continue TZD therapy if the person has had a beneficial metabolic response (>0.5% reduction in $HbA_{1c}$ in six months).<br>• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.<br>• A TZD may be preferable to a DPP-4 inhibitor if:<br>  o The person has marked insulin insensitivity.<br>  o A DPP-4 inhibitor is contraindicated.<br>  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor.<br>• There may be some people for whom either a TZD or a DPP-4 inhibitor may be suitable.<br><br>GLP-1 mimetics<br>• Consider adding a GLP-1 mimetic as third-line therapy to first-line |

| Clinical Guideline | Recommendation(s) |
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| | metformin and a second-line sulfonylurea when control of blood glucose is inadequate ($HbA_{1c}$ ≥7.5%) and the person has:<br>o A body mass index ≥35 kg/m$^2$ in those of European descent (with appropriate adjustment for other ethnic groups), or a BMI <35 kg/m$^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.<br>• Only continue GLP-1 mimetic therapy if the person has had a beneficial metabolic response (>1% reduction in $HbA_{1c}$ and weight loss >3% of initial body weight at six months).<br><br><u>Insulin therapy</u><br>• Begin with human NPH insulin injected at bedtime or twice daily according to need.<br>• Consider using a long-acting insulin analogue if:<br>o The person needs assistance from a caregiver or healthcare professional to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.<br>o The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes.<br>o The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.<br>o The person cannot use the device to inject NPH insulin.<br>• Consider twice-daily pre-mixed (biphasic) human insulin ($HbA_{1c}$ ≥9.0%). A once-daily regimen may be an option.<br>• Consider pre-mixed preparations that include short-acting insulin analogs, rather than pre-mixed preparations that include short-acting human insulin preparations, if:<br>o A person prefers injecting insulin immediately before a meal<br>o Hypoglycemia is a problem.<br>o Blood glucose levels rise markedly after meals.<br>• Consider switching to a long-acting insulin analogue from NPH insulin in people:<br>o Who do not reach their target $HbA_{1c}$ because of significant hypoglycemia.<br>o Who experience significant hypoglycemia on NPH insulin irrespective of the level of $HbA_{1c}$ reached.<br>o Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.<br>o Who need help from a caregiver or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.<br>• Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). |
| National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[16] (2008)** | <u>Metformin</u><br>• Start metformin in overweight or obese patients and whose blood glucose is inadequately controlled by lifestyle interventions alone.<br>• Consider metformin as an option for first-line glucose-lowering therapy for patients who are not overweight.<br>• Continue metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added. |

| Clinical Guideline | Recommendation(s) |
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| | <u>Insulin secretagogues</u><br>• Consider a sulfonylurea as an option for first-line glucose-lowering therapy if the patient is not overweight, the patient does not tolerate metformin (or its contraindicated), or a rapid response to therapy is required because of hyperglycemic symptoms.<br>• Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin.<br>• Continue sulfonylurea therapy if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added.<br>• When adherence is a problem, offer a once-daily, long-acting sulfonylurea.<br><br><u>Rapid-acting insulin secretagogues</u><br>• Consider offering a rapid-acting insulin secretagogue to a patient with an erratic lifestyle.<br><br><u>Acarbose</u><br>• Consider acarbose for a patient unable to use other oral glucose-lowering medications.<br><br><u>TZDs</u><br>• If glucose concentrations are not adequately controlled, consider adding a TZD to:<br>  o The combination of metformin and a sulfonylurea where insulin would otherwise be considered, but is likely to be unacceptable or of reduced effectiveness.<br>  o A sulfonylurea if metformin is not tolerated.<br>  o Metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycemia with sulfonylureas particularly significant.<br><br><u>Gliptins: GLP-1 enhancers</u><br>• No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.<br><br><u>Exenatide: GLP-1 mimetics</u><br>• Exenatide is not recommended for routine use in Type 2 diabetes.<br>• Consider exenatide as an option only if all the following apply for the individual:<br>  o Body mass index >35kg/m$^2$ in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups.<br>  o Specific problems of a psychological, biochemical or physical nature arising from high body weight.<br>  o Inadequate blood glucose control ($HbA_{1c}$ ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea.<br>  o Other therapies, such as a thiazolidinedione or insulin injection therapy, would otherwise be started<br>• Continue exenatide therapy only if a beneficial metabolic response (>1.0% $HbA_{1c}$ reduction in six months and a weight loss of at least 5% at one year) occurs and is maintained.<br><br><u>Insulin therapy</u> |

| Clinical Guideline | Recommendation(s) |
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| | • May be offered to patients with inadequate blood glucose control on optimized oral glucose-lowering agents.<br>• When starting basal insulin therapy:<br>  ○ Continue with metformin and the sulfonylurea (and acarbose, if used)<br>  ○ Review the use of the sulfonylurea if hypoglycemia occurs<br>• When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):<br>  ○ Continue with metformin<br>  ○ Continue the sulfonylurea initially and discontinue if hypoglycemia occurs<br>• Consider combining pioglitazone with insulin therapy for:<br>  ○ Those who have previously had a marked glucose lowering response to thiazolidinedione therapy.<br>  ○ Those on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.<br>• Insulin therapy should be initiated from a choice of a number of insulin types and regimens.<br>• Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.<br>• Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:<br>  ○ Those who require assistance from a care taker or healthcare professional to administer their insulin injections<br>  ○ Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycemic episodes<br>  ○ Those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.<br>• Consider twice-daily biphasic human insulin (pre-mixed) regimens if the $HbA_{1c}$ is >9.0%. A once-daily regimen may be an option when initiating this therapy.<br>• Consider pre-mixed preparations of insulin analogs rather than pre-mixed human insulin preparations when:<br>  ○ Immediate injection before a meal is preferred.<br>  ○ Hypoglycemia is a problem.<br>  ○ There are marked postprandial blood glucose excursions.<br>• Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycemia.<br>• Monitor a person using a basal insulin regimen for the need for mealtime insulin. If blood glucose control remains inadequate, move to a more intensive (mealtimes plus basal insulin) regimen based on the option of human or analogue insulins. |
| Institute for Clinical Systems Improvement (ICSI):<br>**Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[17] (2012)** | • Concurrent initiation of metformin with medical nutrition therapy is recommended for most at the time of diagnosis.<br>• At the time of diagnosis, if the patient has severe symptomatic disease, insulin should be initiated.<br>• Metformin and alpha-glucosidase inhibitors should not be used with renal dysfunction.<br>• Metformin should be used with caution with conditions that predispose patients to the risk of hypoxia.<br>• Metformin and TZDs should not be used if alanine aminotransferase is 2.5 to 3.0 times normal upper limits. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Metformin is the preferred initial oral agent for type 2 diabetes.<br>• If treatment goals are not met with oral antidiabetic agents, or if oral antidiabetic agents are contraindicated, then initiation of insulin, either alone or as an adjunct to oral therapy, is required. |
| International Diabetes Federation (IDF) Clinical Guidelines Task Force: **Global Guideline for Type 2 Diabetes[18] (2005)** | Lifestyle management<br>• Nutrition therapy and physical activity training should be incorporated into diabetes self-management programs.<br><br>Oral therapy<br>• Metformin should be considered first-line therapy, unless contraindicated.<br>• Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients.<br>• When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.<br>• Alpha-glucosidase inhibitors may be considered as a further option.<br><br>Insulin<br>• When oral glucose-lowering agents and lifestyle interventions are unable to maintain blood glucose at target levels, insulin therapy should be started and may include the following regimens:<br>• Basal insulin (e.g., insulin detemir, insulin glargine, or NPH insulin) once daily.<br>• Twice daily premixed (biphasic) insulin, particularly with higher $HbA_{1c.}$<br>• Multiple daily injections (mealtime and basal insulin) in patients that are not controlled on other insulin regimens. |

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the thiazolidinediones are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 3. FDA-Approved Indications for the Thiazolidinediones[1-6]**

| Indication | Single Entity Agents | | Combination Products | | | |
|---|---|---|---|---|---|---|
| | Pio-glitazone | Rosi-glitazone | Pioglitazone and Glimepiride | Pioglitazone and Metformin | Rosiglitazone and Glimepiride | Rosiglitazone and Metformin |
| Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes in multiple clinical settings | ✔ | | | | | |
| Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with pioglitazone and metformin or who have inadequate glycemic control on pioglitazone alone or metformin alone | | | | ✔ | | |
| Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone | | | ✔ | | | |
| Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who either are already taking rosiglitazone or not already taking rosiglitazone and are unable to achieve adequate glycemic control on other diabetes medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons* | | ✔ * | | | | |
| Adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and glimepiride is appropriate in adults with type 2 diabetes who are either already taking rosiglitazone or not already taking rosiglitazone and unable to achieve glycemic control on other diabetes medications and have decided not to take pioglitazone or pioglitazone-containing products for medical reasons | | | | | ✔ * | |
| Adjunct to diet and exercise to improve glycemic | | | | | | ✔ * |

| Indication | Single Entity Agents | | Combination Products | | | |
|---|---|---|---|---|---|---|
| | Pio-glitazone | Rosi-glitazone | Pioglitazone and Glimepiride | Pioglitazone and Metformin | Rosiglitazone and Glimepiride | Rosiglitazone and Metformin |
| control when treatment with both rosiglitazone and metformin is appropriate in adults with type 2 diabetes who are either already taking rosiglitazone or not already taking rosiglitazone and unable to achieve glycemic control on other diabetes medications and have decided not to take pioglitazone or pioglitazone-containing products for medical reasons | | | | | | |

*After consultation with a healthcare professional who has considered and advised the patient of the risk and benefits of rosiglitazone.

## IV. Pharmacokinetics

The pharmacokinetic parameters of the thiazolidinediones are listed in Table 4.

**Table 4. Pharmacokinetic Parameters of the Thiazolidinediones[7]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Excretion (%) | Half-Life (hours) |
|---|---|---|---|---|---|
| **Single Entity Agents** | | | | | |
| Pioglitazone | 50* | >99 | Liver, extensive (% not reported) | Renal (15 to 30) | 3 to 7 |
| Rosiglitazone | 99 | 99.8 | Liver, extensive (% not reported) | Renal (64), Feces (23) | 3 to 4 |
| **Combination Products** | | | | | |
| Pioglitazone and glimepiride | 50*/100 | >99 | Liver, extensive (% not reported) | Renal (15 to 30)/ Renal (60), Feces (40) | 3 to 7/9 |
| Pioglitazone and metformin | 50*/50 to 60† | >99/Negligible (% not reported) | Liver, extensive (% not reported) | Renal (15 to 30)/ Renal (90) | 3 to 7/ 1.5 to 6.2 |
| Rosiglitazone and glimepiride | 99/100 | 99.8/99.5 | Liver, extensive (% not reported) | Renal (64), Feces (23)/Renal (60), Feces (40) | 3 to 4/9 |
| Rosiglitazone and metformin | 99/50 to 60† | 99.8/Negligible (% not reported) | Liver, extensive (% not reported) | Renal (64), Feces (23)/Renal (90) | 3 to 4/ 1.5 to 6.2 |

*Animal studies.
†Immediate-release.

## V. Drug Interactions

Significant drug interactions with the thiazolidinediones are listed in Table 5.

**Table 5. Significant Drug Interactions with the Thiazolidinediones[8]**

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Metformin | 1 | Iodine-containing radiopaque agents | Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis. |
| Sulfonylureas | 1 | Quinolones | The hypoglycemic effect of sulfonylureas may be increased by quinolones especially in elderly patients with renal compromise. Hypoglycemia symptoms including lightheadedness, diaphoresis, tachycardia and various neurologic and psychiatric disturbances may occur. The mechanism of this interaction is unknown. |
| Pioglitazone, rosiglitazone | 2 | Gemfibrozil | Gemfibrozil may inhibit the metabolism of thiazolidinediones and increase plasma concentrations. There is an increased risk of hypoglycemia and other adverse effects. |
| Pioglitazone, rosiglitazone | 2 | Rifamycins | Rifamycins may increase the metabolism of the thiazolidinediones, reducing their plasma concentrations and half-lives, resulting in decreased glycemic control. |

| Generic Name(s) | Significance Level | Interaction | Mechanism |
|---|---|---|---|
| Sulfonylureas | 2 | Azole antifungals | Azole antifungals may inhibit cytochrome P450 2C9-mediated metabolism of sulfonylureas. The hypoglycemic effects of sulfonylureas may be increased by azole antifungals. |
| Sulfonylureas | 2 | Chloramphenicol | Chloramphenicol may reduce hepatic clearance of certain sulfonylureas and cause an increased hypoglycemic response. Symptoms of hypoglycemia: lightheadedness, diaphoresis, tachycardia, and various neurologic and psychiatric disturbances may occur. |
| Sulfonylureas | 2 | Clofibrate | Clofibrate may cause an increased hypoglycemic response to certain sulfonylureas through an unknown mechanism. |
| Sulfonylureas | 2 | Diazoxide | Diazoxide may decrease endogenous insulin release and cause increases in glucose and free fatty acids resulting in a decrease in glycemic control in patients stabilized on a sulfonylurea. |
| Sulfonylureas | 2 | Fenfluramine and derivatives | The hypoglycemic effects of sulfonylureas may be increased by fenfluramine and derivatives. Pharmacologic effects may be additive. |
| Sulfonylureas | 2 | Monoamine oxidase inhibitors (MAOIs) | MAOIs may enhance the hypoglycemic action of sulfonylureas through an unknown mechanism. Monitor blood glucose concentrations and adjust the doses of the sulfonylurea accordingly. |
| Sulfonylureas | 2 | Phenylbutazone | The hypoglycemic effects of sulfonylureas may be increased. Symptoms of hypoglycemia: lightheadedness, diaphoresis, tachycardia, and various neurologic and psychiatric disturbances may occur. |
| Sulfonylureas | 2 | Rifamycins | Rifamycins may decrease the half-life and increase the clearance of sulfonylureas through increased metabolism. |
| Sulfonylureas | 2 | Sulfonamides | Sulfonamides may impair the metabolism of sulfonylureas and enhance the hypoglycemic effects of sulfonylureas. |

Significance Level 1 = major severity
Significance Level 2 = moderate severity

## VI. Adverse Drug Events

The most common adverse drug events reported with the thiazolidinediones are listed in Table 6. The boxed warnings for the thiazolidinediones are listed in Tables 7 through 12. The TZDs are associated with a boxed warning regarding the risk of development or exacerbation of congestive heart failure.[1,2] Rosiglitazone-containing products are associated with an additional boxed warning regarding an increased risk of myocardial infarction. Of note, data from clinical trials do not always support this finding, and there have been no clinical trials directly comparing the cardiovascular risk of pioglitazone and rosiglitazone.[2] Because of the observed adverse cardiovascular outcomes, rosiglitazone-containing products are FDA-approved for the management of type 2

diabetes after consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of therapy. Furthermore, use of rosiglitazone-containing products in patients not already receiving the agent is appropriate for patients who have decided not to take pioglitazone due to medical reasons. Due to the potential increased risk of myocardial infarction, rosiglitazone is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program.[2]

**Table 6. Adverse Drug Events (%) Reported with the Thiazolidinediones[1-6]**

| Adverse Event | Single Entity Agents | | Combination Products | | | |
|---|---|---|---|---|---|---|
| | Pio-glitazone | Rosi-glitazone | Pioglitazone and Glimepiride* | Pioglitazone and Metformin* | Rosiglitazone and Glimepiride* | Rosiglitazone and Metformin* |
| **Cardiovascular** | | | | | | |
| Anemia | | | - | - | - | 7.1 |
| Angina | | ✔ | | | | |
| Congestive heart failure | ✔ | ✔ | | | | |
| Myocardial infarction | | ✔ | | | | |
| Myocardial ischemia | | ✔ | | | | |
| **Central Nervous System** | | | | | | |
| Dizziness | | | - | 4.8 to 5.4 | - | - |
| Headache | 7 to 9 | 6 | 4.0 to 7.1 | 4.6 to 6.0 | - | 6.5 |
| **Endocrine and Metabolic** | | | | | | |
| Aggravated diabetes | 5 | - | - | - | - | - |
| Edema | 5 to 15 | 5 to 15 | 5.7 to 12.3 | 2.9 to 11.3 | - | 4.4 |
| Hyperglycemia | - | 4 | - | - | - | - |
| Hypoglycemia | ✔ | ✔ | 13.4 to 15.7 | - | - | 3 |
| Weight gain | ✔ | ✔ | 9.1 to 13.4 | 2.9 to 6.7 | - | - |
| **Gastrointestinal** | | | | | | |
| Diarrhea | - | 2 | 4.3 to 6.0 | 4.8 to 5.8 | - | 12.7 |
| Nausea | | | 4.0 to 5.1 | 3.6 to 5.8 | - | - |
| Tooth disorder | 5 | - | - | - | - | - |
| Genitourinary | | | | | | |
| Ovulation | ✔ | ✔ | - | - | - | - |
| **Hematologic** | | | | | | |
| Anemia | ≤2 | 2 to 7 | - | - | - | 7.1 |
| Hematocrit decreased | ✔ | ✔ | | | | |
| Hemoglobin decreased | ✔ | ✔ | | | | |
| **Musculoskeletal** | | | | | | |
| Arthralgia | | | - | - | - | 5 |
| Back pain | - | 4 | - | - | - | 5 |
| Fatigue | - | 4 | - | - | - | 5.9 |
| Fracture | 5 | ✔ | - | - | - | - |
| Myalgia | 3 to 5 | - | - | - | - | - |
| **Respiratory** | | | | | | |
| Dyspnea | ✔ | - | - | - | - | - |
| Pharyngitis | 5 | - | - | - | - | - |
| Pleural effusion | - | ✔ | - | - | - | - |
| Pulmonary edema | - | ✔ | - | - | - | - |
| Sinusitis | 6 | 3 | - | 4.4 to 5.0 | - | 6.2 |
| Upper respiratory tract infection | 13 | 10 | 12.3 to 16.6 | 12.4 to 15.5 | - | - |
| **Other** | | | | | | |
| Cholestatic hepatitis | - | ✔ | - | - | - | - |
| Hepatotoxicity | Rare | Rare | - | - | - | - |
| Injury | - | 8 | 3.5 | - | - | 8 |
| Macular edema | ✔ | ✔ | - | - | - | - |
| Pain in limb | - | - | 4.0 to 5.4 | - | - | - |
| Urinary tract infection | - | - | 5.7 to 6.8 | 5.3 to 5.8 | - | 16 |
| Viral infection | - | - | - | - | - | 5 |

*Adverse reactions for combination therapy only are reported.
-Event not reported.
✔ Percent not specified.

**Table 7. Boxed Warning for Actos® (pioglitazone)[1]**

| WARNING |
|---|
| Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of pioglitazone, and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea, and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone in patients with established New York Heart Association class III or IV heart failure is contraindicated. |

**Table 8. Boxed Warning for Duetact® (pioglitazone and glimepiride)[3]**

| WARNING |
|---|
| Thiazolidinediones, including pioglitazone, which is a component of Duetact®, cause or exacerbate congestive heart failure in some patients. After initiation of Duetact®, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation of Duetact® must be considered. Duetact® is not recommended in patients with symptomatic heart failure. Initiation of Duetact® in patients with established New York Heart Association Class III or IV heart failure is contraindicated. |

**Table 9. Boxed Warning for Actoplus Met® (pioglitazone and metformin), Actoplus Met XR® (pioglitazone and metformin extended-release)[4]**

| WARNING |
|---|
| Congestive Heart Failure: Thiazolidinediones, including pioglitazone, which is a component of Actoplus Met® and Actoplus Met XR®, cause or exacerbate congestive heart failure in some patients. After initiation of Actoplus Met® or Actoplus Met XR®, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of Actoplus Met® or Actoplus Met XR® must be considered. Actoplus Met® and Actoplus Met XR® are not recommended in patients with symptomatic heart failure. Initiation of Actoplus Met® or Actoplus Met XR® in patients with established New York Heart Association Class III or IV heart failure is contraindicated.<br><br>Lactic Acidosis: Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, Actoplus Met® or Actoplus Met XR® should be discontinued and the patient hospitalized immediately. |

**Table 10. Boxed Warning for Avandia® (rosiglitazone)[2]**

| WARNING |
|---|
| Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of rosiglitazone, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered. Rosiglitazone is not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone in patients with established New York Heart Association Class III or IV heart failure is contraindicated. A meta-analysis of 52 clinical trials (mean duration six months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with a statistically significant increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction, and a statistically non- |

| WARNING |
| --- |
| significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone and pioglitazone, but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. Because of the potential increased risk of myocardial infarction, rosiglitazone is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com. |

**Table 11. Boxed Warning for Avandaryl® (rosiglitazone and glimepiride)[5]**

| WARNING |
| --- |
| Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of Avandaryl®, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of Avandaryl® must be considered. Avandaryl® is not recommended in patients with symptomatic heart failure. Initiation of Avandaryl® in patients with established New York Heart Association Class III or IV heart failure is contraindicated. A meta-analysis of 52 clinical trials (mean duration six months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial infarction. Three other trials (mean duration 46 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction, and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone and Actos® (pioglitazone, another thiazolidinedione), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. Because of the potential increased risk of myocardial infarction, Avandaryl® is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1800-AVANDIA or visit www.AVANDIA.com. |

**Table 12. Boxed Warning for Avandamet® (rosiglitazone and metformin)[6]**

| WARNING |
| --- |
| Congestive heart failure and myocardial infarction: thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. After initiation of Avandamet®, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of Avandamet® must be considered. Avandamet® is not recommended in patients with symptomatic heart failure. Initiation of Avandamet® in patients with established New York Heart Association Class III or IV heart failure is contraindicated. A meta-analysis of 52 clinical trials (mean duration six months; 16,995 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to some other approved oral antidiabetic agents or placebo, showed a statistically non-significant increased risk of myocardial infarction, and a statistically non-significant decreased risk of death. There have been no clinical trials directly comparing cardiovascular risk of rosiglitazone to Actos® (pioglitazone, another thiazolidinediones), but in a separate trial, pioglitazone (when compared to placebo) did not show an increased risk of myocardial infarction or death. Because of the potential increased risk of myocardial infarction, Avandamet® is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program. Both prescribers and patients need to enroll in the program. To enroll, call 1-800-AVANDIA or visit www.AVANDIA.com.<br>Lactic acidosis: lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. If acidosis is suspected, discontinue Avandamet® and hospitalize the patient immediately. |

## VII. Dosing and Administration

The usual dosing regimens for the thiazolidinediones are listed in Table 13.

**Table 13. Usual Dosing Regimens for the Thiazolidinediones[1-6]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| **Single Entity Agents** | | | |
| Pioglitazone | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes in multiple clinical settings as monotherapy or as combination therapy:<br>Tablet: initial, 15 or 30 mg QD; maximum, 45 mg QD | Safety and efficacy in pediatric patients have not been established. | Tablet:<br>15 mg<br>30 mg<br>45 mg |
| Rosiglitazone | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are either already receiving rosiglitazone or are not already receiving rosiglitazone and are unable to achieve adequate glycemic control on other diabetes medication and have decided not to take pioglitazone for medical reasons:<br>Tablet: initial, 4 mg/day administered as a single dose or in two divided doses; maintenance, 8 mg/day; maximum, 8 mg/day | Safety and efficacy in pediatric patients have not been established. | Tablet:<br>2 mg<br>4 mg<br>8 mg |
| **Combination Products** | | | |
| Pioglitazone and glimepiride | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone:<br>Tablet: initial, based on patient's current regimen of pioglitazone and/or sulfonylurea, administer QD | Safety and efficacy in pediatric patients have not been established. | Tablet:<br>30-2 mg<br>30-4 mg |
| Pioglitazone and metformin | Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with pioglitazone and metformin or who have inadequate glycemic control on pioglitazone alone or metformin alone:<br>Extended-release tablet: initial, based on patient's current regimen of pioglitazone and/or metformin, administer QD; maximum, 45-2,000 mg/day<br><br>Tablet: initial, based on patient's current regimen of pioglitazone and/or metformin; maximum, 45-2,550 mg/day | Safety and efficacy in pediatric patients have not been established. | Extended-release tablet:<br>15-1,000 mg<br>30-1,000 mg<br><br>Tablet:<br>15-500 mg<br>15-850 mg |
| Rosiglitazone and glimepiride | Adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and glimepiride is appropriate in adults with type 2 diabetes who are either already taking rosiglitazone or not already taking rosiglitazone and unable to achieve glycemic control on other diabetes | Safety and efficacy in pediatric patients have not been established. | Tablet:<br>4-1 mg<br>4-2 mg<br>4-4 mg<br>8-2 mg<br>8-4 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | medications and have decided not to take pioglitazone or pioglitazone-containing products for medical reasons<br>Tablet: initial, 4-1 or 4-2 mg QD; maximum, 8-4 mg/day | | |
| Rosiglitazone and metformin | Adjunct to diet and exercise to improve glycemic control when treatment with both rosiglitazone and metformin is appropriate in adults with type 2 diabetes who are either already taking rosiglitazone or not already taking rosiglitazone and unable to achieve glycemic control on other diabetes medications and have decided not to take pioglitazone or pioglitazone-containing products for medical reasons:<br>Tablet: initial, based on patient's current regimen of rosiglitazone and/or metformin, administer in divided doses; maximum, 8-2,000 mg/day | Safety and efficacy in pediatric patients have not been established. | Tablet:<br>2-500 mg<br>2-1,000 mg<br>4-500 mg<br>4-1,000 mg |

QD=once daily

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazolidinediones are summarized in Table 14.

**Table 14. Comparative Clinical Trials with the Thiazolidinediones**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Cardiovascular Outcomes Trials** | | | | |
| Dormandy et al.[19] (2005)<br><br>Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated<br><br>vs<br><br>placebo<br><br>Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications. | DB, MC, PC, PRO, RCT<br><br>Patients 35 to 75 years of age with type 2 diabetes and an $HbA_{1c}$ >6.5% despite treatment with diet alone or with oral glucose-lowering agents with or without insulin and evidence of extensive macrovascular disease as defined by ≥1 of the following: MI or stroke at least 6 months prior to enrollment, percutaneous coronary intervention or coronary artery bypass surgery at least 6 months prior to enrollment, acute coronary syndrome at least 3 months prior to enrollment, | N=5,238 (n=2,605 for pioglitazone; n=2,633 for placebo)<br><br>34.5 months (average time of observation) | Primary:<br>Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle<br><br>Secondary:<br>Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke (main secondary end point); cardiovascular death; and time to individual components of the primary composite | Primary:<br>At least one event in the primary composite end point occurred in 514 patients taking pioglitazone and 572 patients taking placebo (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).<br><br>Secondary:<br>Fewer patients on pioglitazone reached the main secondary end point (composite of all-cause mortality, MI and stroke) compared to patients on placebo (301 vs 358 patients; HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027).<br><br>Significantly more reports of heart failure were noted in patients treated with pioglitazone compared to patients treated with placebo (281 vs 198 patients; P<0.0001). Deaths due to heart failure did not differ significantly between the two study groups (25 for pioglitazone vs 22 for placebo; P=0.634).<br><br>A greater number of patients on pioglitazone reported edema without heart failure compared to those on placebo (562 vs 341; P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | or objective evidence of coronary artery disease or obstructive arterial disease in the leg; patients were excluded if they had type 1 diabetes; were taking insulin only; had planned coronary or peripheral revascularization; had NYHA class II heart failure or above; had ischemic ulcers, gangrene or rest pain in the leg; had had hemodialysis; or had 2.5 times or greater the upper limit of normal concentrations of ALT | | end point | |
| Wilcox et al.[20] (2007)<br><br>Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated | DB, MC, PC, PRO, RCT<br><br>Comparison of patients with and without prior stroke enrolled in the PROactive Study (see above) | N=5,238 (n=984 patients with prior stroke; n=4,254 patients without prior stroke)<br><br>34.5 months (average time | Primary:<br>Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical | Primary:<br>In patients with prior stroke (n=486 pioglitazone and n=498 placebo), there was a trend of benefit with pioglitazone compared to placebo for the primary end point of all-cause mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle (event rate, 20.2% pioglitazone vs 25.3% placebo; HR, 0.78; 95% CI, 0.60 to 1.02; P=0.0670).<br><br>Secondary:<br>In patients with prior stroke, there was a trend of benefit with pioglitazone |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>placebo<br><br>Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications. | | of observation) | intervention on coronary or leg arteries, or amputation above the ankle<br><br>Secondary:<br>Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke | compared to placebo for the main secondary end point of all-cause mortality, nonfatal MI or nonfatal stroke (event rate, 15.6% with pioglitazone vs 19.7% with placebo; HR, 0.78; 95% CI, 0.58 to 1.06; P=0.1095).<br><br>In patients with prior stroke, pioglitazone reduced fatal or nonfatal stroke (event rate, 5.6% pioglitazone vs 10.2% placebo; HR, 0.53; 95% CI, 0.34 to 0.85; P=0.0085) and the composite of cardiovascular death, nonfatal MI or nonfatal stroke (event rate, 13.0% with pioglitazone vs 17.7% with placebo; HR, 0.72; 95% CI, 0.52 to 1.00; P=0.0467).<br><br>Higher event rates were observed in patients with prior stroke compared to those without prior stroke. In patients without prior stroke, no treatment effect was observed for a first stroke.<br><br>In a subgroup analysis from PROactive, pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with type 2 diabetes. |
| Erdmann et al.[21] (2007)<br><br>Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated<br><br>vs<br><br>placebo<br><br>Study drugs were taken in addition to the patients' glucose-lowering drugs and other | DB, MC, PC, PRO, RCT<br><br>Patients who qualified for entry into the PROactive Study on the basis of a previous MI 6 months or more before randomization (see above) | N=2,445 patients with prior MI (n=1,230 in the pioglitazone group; n=1,215 in the placebo group)<br><br>34.5 months (average time of observation) | Primary:<br>Fatal or nonfatal MI (excluding silent MI); cardiovascular death or nonfatal MI; cardiovascular death, nonfatal MI or stroke; see PROactive Study<br><br>Secondary:<br>Acute coronary syndrome; composite of nonfatal MI (excluding silent MI), coronary revascularization, acute coronary | Primary:<br>Pioglitazone significantly reduced the risk of fatal and nonfatal MI (RR, 28%; P=0.045).<br><br>There were no significant differences in the end point of cardiovascular death or nonfatal MI (P=0.201) or the end point of cardiovascular death, nonfatal MI or stroke (P=0.149).<br><br>Secondary:<br>Pioglitazone significantly reduced the risk of acute coronary syndrome (RR, 37%; P=0.035).<br><br>Pioglitazone significantly reduced the risk of the cardiac composite end point of nonfatal MI, coronary revascularization, acute coronary syndrome and cardiac death (RR, 19%; P=0.033).<br><br>PROactive:<br>The differences in the primary and main secondary end points defined in the main PROactive study did not reach significance in the MI population (P=0.135 and P=0.0585, respectively); however, there was a consistently |

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| medications. | | | syndrome, or cardiac death; see PROactive Study | lower number of events in the pioglitazone-treated patients for all of the end points.<br><br>The rate of heart failure and heart failure requiring hospitalization (in patients with a previous MI) were significantly higher in the pioglitazone group compared to the placebo group (13.5 vs 9.6%; P=0.003 and 7.5 vs 5.2%; P=0.022, respectively). The rates of fatal heart failure were similar (1.4% with pioglitazone vs 0.9% with placebo; P=0.283). |
| Erdmann et al.[22] (2007)<br><br>Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated<br><br>vs<br><br>placebo<br><br>Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications. | DB, MC, PC, PRO, RCT<br><br>Patients enrolled into the PROactive study who developed serious heart failure (defined as heart failure that required hospitalization or prolonged a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity) (see above); patients with NYHA Class II-IV heart failure at screening were excluded | N=5,238<br><br>34.5 months (average time of observation) | Primary:<br>Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle<br><br>Secondary:<br>Composite of all-cause mortality, nonfatal MI and nonfatal stroke | Primary:<br>Among patients with a serious heart failure event, subsequent all-cause mortality was proportionately lower with pioglitazone (40 of 149 [26.8%] vs 37 of 108 [34.3%] with placebo; P=0.1338). Proportionately fewer pioglitazone patients with serious heart failure went on to have an event in the primary end point (47.7% with pioglitazone vs 57.4% with placebo; P=0.0593).<br><br>Secondary:<br>More pioglitazone (5.7%) than placebo patients (4.1%) had a serious heart failure event during the study (P=0.007). However, mortality due to heart failure was similar (25 of 2,605 [0.96%] for pioglitazone vs 22 of 2,633 [0.84%] for placebo; P=0.639).<br><br>Significantly fewer pioglitazone patients with serious heart failure went on to have an event in the main secondary end point (34.9% with pioglitazone vs 47.2% with placebo; P=0.025). |
| Wilcox et al.[23] (2008)<br><br>Pioglitazone 15 mg (month 1) QD | DB, MC, PC, RCT (PROactive 10 Study)<br><br>Patients 35 to 75 | N=5,238<br><br>34.5 months (average time of | Primary:<br>Analysis of the prespecified main secondary end point (MACE) and | Primary:<br>Pioglitazone was associated with a 16% reduction in the main secondary end point of MACE compared to placebo (P=0.027).<br><br>In the pioglitazone group, 9.9% of patients experienced an event from the |

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| titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated<br><br>vs<br><br>placebo<br><br>Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications. | years of age with type 2 diabetes, $HbA_{1c}$ >6.5% despite treatment with diet or oral antidiabetic agents with or without insulin, and extensive macrovascular disease | observation) | additional MACE end points (MACE1 through MACE 7) (MACE=all-cause mortality, nonfatal MI, nonfatal stroke; MACE1=cardio-vascular mortality, nonfatal MI, or nonfatal stroke; MACE2=all-cause mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE3=cardio-vascular mortality, nonfatal MI, nonfatal stroke, acute coronary syndrome; MACE4=cardiac mortality, nonfatal MI, nonfatal stroke; MACE5=cardiac mortality, nonfatal MI, acute coronary syndrome; MACE6=cardiac mortality, nonfatal MI, nonfatal stroke, acute coronary | MACE1 composite end point compared to 11.9% of patients receiving placebo (HR, 0.82; 95% CI, 0.70 to 0.97; P=0.0201).<br><br>Fewer patients receiving pioglitazone experienced an event from the MACE2 end point compared to placebo (HR, 0.83; 95% CI, 0.72 to 0.96; P=0.0103). A similar result was observed for other end points, including MACE3 (P=0.0051), MACE4 (P=0.0120), MACE5 (P=0.0132), and MACE6 (P=0.0034). There was no significant difference in the MACE7 end point.<br><br>Secondary:<br>Not reported |

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| | | | syndrome; MACE7=cardiac mortality, nonfatal MI<br><br>Secondary:<br>Not reported | |
| Home et al.[24] (2007)<br><br>Rosiglitazone plus either metformin or a sulfonylurea<br><br>vs<br><br>metformin plus a sulfonylurea | MC, OL, RCT<br><br>Patients with type 2 diabetes between 40 and 75 years of age, BMI >25.0 kg/m$^2$, $HbA_{1c}$ 7.1 to 9.0% while receiving maximum permitted or tolerated doses of metformin or a sulfonylurea; exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension | N=4,447 (n=1,117 rosiglitazone plus metformin; n=1,103 rosiglitazone plus sulfonylurea; n=2,227 metformin plus sulfonylurea)<br><br>Mean follow-up 3.75 years for the unplanned interim analyses (study was designed to be 6 years) | Primary:<br>Hospitalization or death from cardiovascular causes<br><br>Secondary:<br>Death from cardiovascular causes and from any cause, MI, congestive heart failure, and composite of death from cardiovascular causes, MI and stroke | Primary:<br>For adjudicated primary end points (hospitalization or death from cardiovascular causes), the HR was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication.<br><br>Secondary:<br>There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI.<br><br>Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006). |
| Home et al.[25] | MC, OL, RCT | N=4,458 | Primary: | Primary: |

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| (2009)<br><br>Rosiglitazone plus either metformin or a sulfonylurea<br><br>vs<br><br>metformin plus a sulfonylurea | Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | 5.5 years (mean follow-up) | Time to first cardiovascular hospitalization or cardiovascular death<br><br>Secondary: Cardiovascular death, all-cause mortality, MI, stroke, composite of cardiovascular death, MI, and stroke | The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 patients receiving rosiglitazone and active control, respectively (HR, 0.99; 95% CI, 0.85 to 1.16; P=0.93).<br><br>Secondary:<br>There was no significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR, 0.84; 95%, CI 0.59 to 1.18; P=0.32), all-cause mortality (HR, 0.86; 95% CI, 0.68 to 1.08; P=0.19), MI (HR, 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR, 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of cardiovascular death, MI, or stroke (HR, 0.93; 95% CI, 0.74 to 1.15; P=0.50).<br><br>Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR, 2.10; 95% CI, 1.35 to 3.27; P=0.0010).<br><br>There were no serious adverse event reports of macular edema. The incidence of bone fractures was higher with rosiglitazone compared to active control (RR, 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR, 1.82; 95% CI, 1.37 to 2.41 vs RR, 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR, 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR, 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures. |
| Lincoff et al.[26] (2007)<br><br>Pioglitazone monotherapy<br><br>vs<br><br>metformin, placebo, sulfonylureas or | DB, MA, RCT with placebo or active comparator<br><br>Adult patients with type 2 diabetes and inadequate glycemic control | N=16,390 (19 trials)<br><br>4 months to 3.5 years | Primary: Composite of death from any cause, MI or stroke<br><br>Secondary: Incidence of serious heart failure | Primary:<br>Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005).<br><br>Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death: HR, 0.92; P=0.38, MI: HR, 0.81; P=0.08, death and MI: HR, 0.85; P=0.04, and stroke: HR, 0.80; P=0.09).<br><br>Progressive separation of time-to-event curves became apparent after |

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| rosiglitazone<br><br>or<br><br>pioglitazone combination therapy with insulin, metformin, or sulfonylureas<br><br>vs<br><br>active comparator or placebo | | | | approximately one year of therapy.<br><br>Secondary:<br>Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control treated patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17). |
| Richter et al.[27] (2006)<br><br>Pioglitazone monotherapy<br><br>vs<br><br>acarbose, metformin, placebo, repaglinide, rosiglitazone, sulfonylurea<br><br>or<br><br>pioglitazone combination therapy<br><br>vs | MA of DB (15) or OL (4) RCTs (last search conducted in August 2006, included PROactive Study), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | 22 trials<br><br>N=6,200 randomized to pioglitazone treatment (total N not reported)<br><br>24 weeks to 34.5 months | Primary:<br>Patient-oriented outcomes including mortality, morbidity and adverse effects<br><br>Secondary:<br>Health-related quality of life and $HbA_{1c}$ | Primary:<br>Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095).<br><br>Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The individual components of the primary composite end point did not disclose statistically significant differences between the intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6 vs 4% on placebo; P=0.007).<br><br>The percentage of overall and serious adverse events was comparable between the intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between -0.50 and- 0.75 g/dL. Fifteen trials |

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| combination therapy not containing pioglitazone | | | | evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; seven trials described a rise in BMI up to 1.5 $kg/m^2$. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia (P value not reported). The RR for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled.<br><br>Secondary:<br>No study investigated health-related quality of life.<br><br>Active glucose-lowering compounds like metformin, glibenclamide‡, gliclazide* or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to pioglitazone treatment (P values not reported). |
| Mannucci et al.[28] (2008)<br><br>Pioglitazone<br><br>vs<br><br>active comparators, placebo, no treatment | MA (94 trials)<br><br>Patients treated with pioglitazone (with or without type 2 diabetes) | N=21,180<br><br>Variable duration | Primary:<br>All-cause mortality, non-fatal coronary event (defined as MI, unstable angina or coronary revascularization), non-fatal chronic heart failure requiring hospitalization<br><br>Secondary:<br>Not reported | Primary:<br>In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality (P value not reported).<br><br>In non-diabetic patients, only one death was observed occurring among pioglitazone-treated patients.<br><br>In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR, 0.41; 95% CI, 0.23 to 0.72).<br><br>When analyzing all trials, no significant reduction of mortality was observed with pioglitazone.<br><br>Comparing different agents, pioglitazone was associated with a lower mortality rate compared to sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars, or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR, 0.22; 95% CI, 0.05 to 1.03), metformin (RR, 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR, 0.49; 95% CI, 0.04 to 5.36), glitazars (RR, 0.42; 95% CI, 0.11 to 1.61), or placebo (RR, 0.16; 95% CI, 0.02 to 1.45). |

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| | | | | In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events (P value not reported).<br><br>In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported.<br><br>In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR, 0.82; 95% CI, 0.55 to 1.23).<br><br>Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant.<br><br>In PROactive, pioglitazone was associated with an increased risk for chronic heart failure. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR ,1.32; 95% CI, 0.88 to 1.98).<br><br>Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not significant (P value not reported). When adding PROactive or excluding trials vs dual PPARα/γ agonists pioglitazone was associated with a significant increase of risk for chronic heart failure.<br><br>In comparison with different agents, pioglitazone was associated with an increased risk of chronic heart failure in PC trials, while differences with sulfonylureas or glitazars did not reach significance.<br><br>Secondary:<br>Not reported |
| Nagajothi et al.[29] (2008)<br><br>Pioglitazone<br><br>vs | MA (5 trials)<br><br>Patients treated with pioglitazone | N=not reported<br><br>Duration varied | Primary:<br>MI<br><br>Secondary:<br>Stroke, revascularization, | Primary:<br>The RR for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17).<br><br>Secondary:<br>The RR for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07). |

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| active comparators (metformin and/or sulfonylurea) or placebo | | | total mortality, cardiovascular mortality | The RR for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56).<br><br>The RR for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11.<br><br>The RR for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47). |
| Nissen et al.[30] (2007)<br><br>Rosiglitazone monotherapy or combination therapy<br><br>vs<br><br>monotherapy or combination therapy with gliclazide*, glimepiride, glipizide, glyburide, insulin, metformin, placebo | MA of RCTs of more than 24 weeks that had outcome data for MI and death from cardiovascular causes (included ADOPT and DREAM trials)<br><br>Mean age of participants was 56 years, mean baseline $HbA_{1c}$ 8.2% | 42 trials<br><br>n=15,560 for rosiglitazone; n=12,283 for comparator<br><br>24 to 208 weeks | Primary:<br>MI and death from cardiovascular causes<br><br>Secondary:<br>Not reported | Primary:<br>Rosiglitazone was associated with a significant increase in the risk of MI compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03).<br><br>Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06).<br><br>Although not a prespecified end point, the OR for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24).<br><br>Secondary:<br>Not reported |
| Singh et al.[31] (2007)<br><br>Rosiglitazone<br><br>vs<br><br>placebo or other non-TZD oral hypoglycemic | MA of RCTs (available up to May 2007 and included ADOPT, DREAM and RECORD trials) of rosiglitazone of at least 12 months duration | 4 trials<br><br>N=14,291 (n=6,421 rosiglitazone; n=7,870 control)<br><br>1 to 4 years | Primary:<br>RR of MI, heart failure, and cardiovascular mortality<br><br>Secondary:<br>Not reported | Primary:<br>Rosiglitazone significantly increased the risk of MI (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control.<br><br>There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53).<br><br>Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; |

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| agent (including glyburide or metformin) | Study participants with impaired glucose tolerance or type 2 diabetes, studies monitored cardiovascular adverse events and provided numerical data on all adverse events | | | 95% CI, 0.80 to 1.23; P=0.92).<br><br>Secondary:<br>Not reported |
| Richter et al.[32] (2007)<br><br>Rosiglitazone monotherapy<br><br>vs<br><br>glyburide, metformin, pioglitazone, placebo, repaglinide<br><br>or<br><br>rosiglitazone combination therapy<br><br>vs<br><br>combination therapy not containing rosiglitazone | MA of DB (11) or OL (5) RCTs (last search conducted in April 2007, included the ADOPT trial), PG<br><br>Adults with type 2 diabetes, trial duration of at least 24 weeks | 18 trials<br><br>N=3,888 randomized to rosiglitazone treatment (total N not reported)<br><br>24 weeks to 4 years (median 26 weeks) | Primary:<br>Patient-oriented outcomes including mortality, morbidity and adverse effects<br><br>Secondary:<br>Health-related quality of life and metabolic control ($HbA_{1c}$) | Primary:<br>No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group (P values not reported in this reference).<br><br>The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups (P values were not reported in this reference). Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4/4.3% and 1.8/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2/4.0% with metformin; P values were not reported in this reference). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than patients receiving glyburide (0.6%) but not metformin (1.3%; P values were not reported in this reference).<br><br>The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6 vs 4% in the control groups; P value not reported). Median discontinuation rate following rosiglitazone administration was also higher than after control therapy (median of 7 vs 4%; P value not reported). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active |

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| | | | | compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; four studies described a rise in BMI up to 1.5 kg/m$^2$. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of nine studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01).<br><br>Secondary:<br>No study investigated health-related quality of life.<br><br>Active glucose-lowering compounds like metformin, glibenclamide‡ or glimepiride resulted in similar reductions of $HbA_{1c}$ compared to rosiglitazone treatment. |
| Lago et al.[33] (2007)<br><br>Pioglitazone 15 to 45 mg per day or rosiglitazone 4 to 8 mg per day<br><br>vs<br><br>placebo, glibenclamide‡, glimepiride, metformin, metformin plus sulfonylurea | MA of DB, RCTs of TZDs that reported risk estimates or frequency data for congestive heart failure and cardiovascular death<br><br>Patients with prediabetes or type 2 diabetes (with and without cardiovascular disease), mean age 59.2 years, mean BMI 31 kg/m$^2$, mean baseline $HbA_{1c}$ 7.72% | 7 trials<br><br>N=20,191<br><br>29.7 months (range, 12 to 48 months) | Primary:<br>Development of congestive heart failure, risk of cardiovascular death<br><br>Secondary:<br>Not reported | Primary:<br>Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had congestive heart failure events (214 with TZDs and 146 with comparators). The overall event rate for congestive heart failure was 2.3% for patients receiving TZDs and 1.4% in the comparator group.<br><br>Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of congestive heart failure across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07).<br><br>The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI, 0.63 to 1.32; P=0.63) or both TZDs (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both |

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| | | | | drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96).<br><br>Secondary:<br>Not reported |
| Karter et al.[34] (2005)<br><br>Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies | Cohort study of all patients in the Kaiser Permanente Medical Care Program with type 2 diabetes (Kaiser Permanente Northern California Diabetes Registry) who initiated any new diabetes pharmacotherapy between October 1999 and November 2001 | N=23,440<br><br>10.2 months (mean) | Primary:<br>Time-to-incident admission to hospital for congestive heart failure<br><br>Secondary:<br>Not reported | Primary:<br>Three hundred and twenty admissions for congestive heart failure were observed during the follow-up (mean, 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for congestive heart failure in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99).<br><br>Secondary:<br>Not reported |
| Gerrits et al.[35] (2007)<br><br>Pioglitazone<br><br>vs<br><br>rosiglitazone | RETRO cohort study<br><br>Patients median age 56 years who were initiated treatment with pioglitazone or rosiglitazone between 2003 and 2006 | N=29,911 (n=14,807 pioglitazone; n=15,104 rosiglitazone)<br><br>1.2 to 1.3 years | Primary:<br>Risk of hospitalization for acute MI<br><br>Secondary:<br>Risk of composite of acute MI or coronary revascularization | Primary:<br>Among the patients that initiated pioglitazone, 1.1% of patients were hospitalized for acute MI during follow-up compared to 1.4% for rosiglitazone (no P value reported). The unadjusted HR for hospitalization for acute MI associated with pioglitazone relative to rosiglitazone was 0.82 (95% CI, 0.67 to 1.01; P value not reported). After readjustment for baseline covariants (e.g., medical conditions, procedures and dispensed drugs), the HR was 0.78 (95% CI, 0.63 to 0.96; P value not reported).<br><br>Secondary:<br>There were 2.6 and 3.1% of patients in the pioglitazone and rosiglitazone groups, respectively, with a first event in the composite end point of acute MI or coronary revascularization. The adjusted HR for the composite of acute MI or coronary revascularization was 0.85 (95% CI, 0.75 to 0.98; P value not reported). |
| Lipscombe et al.[36] (2007) | Nested case-control analysis of a RETRO cohort | N=159,026<br><br>Median | Primary:<br>Emergency department visit or | Primary:<br>Current treatment with TZD monotherapy was associated with a significantly increased risk of congestive heart failure (78 cases; adjusted |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Pioglitazone or rosiglitazone<br><br>vs<br><br>other oral hypoglycemic agents | study using health care databases in Ontario, Canada<br><br>Diabetes patients 66 years of age or older treated with at least 1 oral hypoglycemic agent between 2002 and 2005, follow-up until March 31, 2006 | follow-up 3.8 years | hospitalization for congestive heart failure<br><br>Secondary: Emergency department visit or hospitalization for acute MI, all-cause mortality | RR, 1.60; 95% CI, 1.21 to 2.10; P<0.001) compared to other oral hypoglycemic agent combination therapies (3,478 congestive heart failure cases).<br><br>The increased risk of congestive heart failure associated with TZD use appeared limited to rosiglitazone.<br><br>Secondary:<br>Current treatment with TZD monotherapy was associated with a significantly increased risk of acute MI (65 vs 3,695 cases; RR, 1.40; 95% CI, 1.05 to 1.86; P=0.02) and death (102 vs 5,529 cases; RR, 1.29; 95% CI, 1.02 to 1.62; P=0.03) compared to other oral hypoglycemic agent combination therapies. |
| Saenz et al.[37] (2005)<br><br>Metformin monotherapy<br><br>vs<br><br>placebo, sulfonylureas, TZDs, meglitinides, α-glucosidase inhibitors, diet, any other oral antidiabetic intervention, insulin | MA (29 RCTs)<br><br>Adult patients with type 2 diabetes | N=5,259<br><br>≥3 months | Primary:<br>Incidence of any diabetes-related outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, heart failure, stroke, renal failure, amputation [of at least one digit], vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); diabetes-related death (death from MI, stroke, | Primary:<br>Obese patients receiving metformin showed a greater benefit than chlorpropamide, glibenclamide*, or insulin for any diabetes-related outcomes (P=0.009) and for all-cause mortality (P=0.03).<br><br>Obese patients receiving metformin showed a greater benefit than overweight patients on conventional treatment (diet) for any diabetes-related outcomes (P=0.004), diabetes-related death (P=0.03), all cause mortality (P=0.01), and MI (P=0.02).<br><br>Secondary:<br>Patients receiving metformin monotherapy showed a significant benefit for glycemic control, weight, dyslipidemia, and DBP. Metformin presents a strong benefit for $HbA_{1c}$ when compared to diet and placebo. Additionally, metformin showed a moderate benefit for glycemic control, LDL-C, and BMI or weight when compared to sulfonylureas. |

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| | | | peripheral vascular disease, renal disease, hypo-glycemia or hyperglycemia, and sudden death); all-cause mortality<br><br>Secondary:<br>Changes in $HbA_{1c}$, FPG, quality of life, weight, BMI, lipids, insulin, C-peptide, BP, micro-albuminuria, glomerular filtration rate, renal plasma flow | |
| **Type 2 Diabetes – Monotherapy** | | | | |
| Khan et al.[38] (2002)<br><br>Pioglitazone 15 to 45 mg QD<br><br>vs<br><br>rosiglitazone 2 to 4 mg QD or 4 mg BID | OL, PRO, RCT<br><br>Patients previously stabilized on troglitazone* with stable liver function, baseline $HbA_{1c}$ 7.9% for pioglitazone and 8.0% for rosiglitazone | N=186<br><br>4 months | Primary:<br>Change in body weight, $HbA_{1c}$, and lipoproteins<br><br>Secondary:<br>Not reported | Primary:<br>Both groups experienced equal and significant weight gain of ~2 kg from baseline (P<0.01).<br><br>No significant change in $HbA_{1c}$ from baseline or difference between groups was observed after four months.<br><br>Pioglitazone had significant reductions in TC (~ -20 mg/dL†) compared to rosiglitazone (~5 mg/dL†; P<0.01).<br><br>Pioglitazone had significant reductions in LDL-C (~ -16 mg/dL†) compared to rosiglitazone (~2 mg/dL†; P<0.01).<br><br>Secondary:<br>Not reported |
| Goldberg et al.[39] (2005) | DB, MC, PG, PRO, RCT | N=802<br><br>24 weeks | Primary:<br>Change in TG, lipoproteins, and | Primary:<br>TG levels significantly decreased (-51.9 mg/dL) with pioglitazone while TG levels increased with rosiglitazone (13.1 mg/dL; P<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Pioglitazone 30 mg QD, titrated to 45 mg QD after 12 weeks<br><br>vs<br><br>rosiglitazone 4 mg QD, titrated to 4 mg BID after 12 weeks | Patients >35 years of age with type 2 diabetes with $HbA_{1c}$ >7.0%, TG ≥150 mg/dL, LDL-C ≤130 mg/dL and C-peptide ≥1 ng/mL; baseline $HbA_{1c}$ 7.6% for pioglitazone and 7.5% for rosiglitazone; patients were excluded if they had NYHA class III-IV heart failure, MI or stroke in past 6 months; liver disease; serum creatinine >2 mg/dL; receiving renal dialysis or having renal transplant; current glucocorticoid use; receiving any lipid-lowering medication, insulin, combination oral antidiabetic therapy or weight loss agent; pregnant or breast feeding; receiving therapy for malignancy; or drug or alcohol abuse | | $HbA_{1c}$; safety<br><br>Secondary:<br>Not reported | Pioglitazone significantly increased HDL-C (5.2 mg/dL) compared to rosiglitazone (2.4 mg/dL; P<0.001).<br><br>Non-HDL-C was significantly higher with rosiglitazone (25.7 mg/dL) compared to pioglitazone (3.6 mg/dL; P<0.001).<br><br>Both treatment groups increased LDL-C, however, smaller increases were observed with pioglitazone (12.3 vs 21.3 mg/dL; P<0.001).<br><br>LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone (P<0.001). LDL particle size increased more with pioglitazone (P=0.005).<br><br>Similar reductions in $HbA_{1c}$ were observed with pioglitazone (-0.7%) and rosiglitazone (-0.6%; P=0.129).<br><br>No difference between agents was observed in adverse events including edema, heart failure, liver function tests, BP, and hypoglycemic episodes.<br><br>Similar weight gain was observed with pioglitazone (2.0 kg) and rosiglitazone (1.6 kg; P=0.164).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| Tran et al.[40] (2006)<br><br>Pioglitazone 45 mg daily<br><br>vs<br><br>rosiglitazone 8 mg daily | RETRO<br><br>Chart review of type 2 diabetic patients who received a TZD for >4 months after inadequate glycemic control on maximally tolerated doses of metformin and a sulfonylurea, baseline $HbA_{1c}$ 9.5% for pioglitazone and 9.3% for rosiglitazone | N=104<br><br>1 year | Primary:<br>Proportion of patients with $HbA_{1c}$ ≤7.5% at four and 12 months<br><br>Secondary:<br>Not specified | Primary:<br>After four months, 62% of patients on pioglitazone (35 total) and 65% of patients on rosiglitazone (31 total) achieved an $HbA_{1c}$ ≤7.5% (P value not reported). Mean $HbA_{1c}$ levels were 7.4% for pioglitazone and 7.5% for rosiglitazone.<br><br>Of the original population with an $HbA_{1c}$ ≤7.5% at four months, 63% of patients on pioglitazone (22 total) and 61% of patients on rosiglitazone (19 total) maintained an $HbA_{1c}$ ≤7.5% after one year (P value not reported).<br><br>Secondary:<br>Not specified |
| Derosa et al.[41] (2004)<br><br>Pioglitazone 15 mg once daily<br><br>vs<br><br>rosiglitazone 4 mg once daily | DB, MC, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes and metabolic syndrome, poor glycemic control ($HbA_{1c}$ >7.5%) or experienced adverse effects with diet and oral hypoglycemic agents, such as sulfonylureas or metformin, administered up to maximum tolerated dose | N=87<br><br>12 months | Primary:<br>Change in baseline BMI, $HbA_{1c}$, FPG, PPG, fasting plasma insulin, postprandial plasma insulin, HOMA index, lipid profile, and lipoprotein variables; safety<br><br>Secondary:<br>Not reported | Primary:<br>Patients in the pioglitazone and rosiglitazone groups experienced a significant increase in mean BMI at 12 months compared to baseline (4.92 and 6.17%, respectively; both P<0.05).<br><br>At 12 months, there was a 1.3% improvement from baseline in mean values for $HbA_{1c}$ (P<0.01), 19.3% in FPG (P<0.01), 16.3% in PPG (P<0.01), 42.4% in fasting plasma insulin (P<0.05), and 23.3% in postprandial plasma insulin (P<0.05); no significant differences were found between treatment groups. Significant improvements in mean HOMA index were also observed in both groups compared to baseline (both P<0.01).<br><br>Patients receiving pioglitazone experienced a significant improvement at 12 months in almost all variables of lipid metabolism from baseline including TC (-11%), LDL-C (-12%), HDL-C (15%), and Apo B (-10.6%; all P<0.05). Patients receiving rosiglitazone experienced a significant increase in TC (14.9%), LDL-C (16.5%), TG (17.9%), and Apo B (10.3%; all P<0.05).<br><br>Of the 87 patients who completed the study, three out of 45 patients in the |

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| | | | | pioglitazone group and five out of 42 patients in the rosiglitazone group had transient, mild-to-moderate adverse events that did not cause withdrawal from the trial.<br><br>Secondary:<br>Not reported |
| Derosa et al.[42] (2006)<br><br>Pioglitazone 15 mg QD<br><br>vs<br><br>rosiglitazone 4 mg QD | DB, MC, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes and metabolic syndrome, poor glycemic control ($HbA_{1c}$ >7.5%) or experienced adverse effects with diet and metformin, administered up to maximum tolerated dose | N=96<br><br>12 months | Primary:<br>Change in baseline BMI, $HbA_{1c}$, lipid profile, lipoprotein (a), and homocysteine<br><br>Secondary:<br>Change in baseline FPG, PPG, and HOMA index | Primary:<br>No BMI change was observed at three, six, nine and 12 months in either group. There was no difference in BMI value between pioglitazone and rosiglitazone (P value not reported).<br><br>Significant $HbA_{1c}$ decreases were observed at nine (both P<0.05 vs baseline) and 12 months (both P<0.01 vs baseline) in both groups.<br><br>Significant TC, LDL-C, HDL-C, and TG improvement was present in the pioglitazone group at 12 months compared to the baseline values, and these variations were significantly different than rosiglitazone (P<0.05). No TC, LDL-C, HDL-C, or TG improvement was present in the rosiglitazone group after 12 months.<br><br>Significant lipoprotein (a) and homocysteine improvement was present in the pioglitazone group at 12 months compared to the baseline values (both P<0.05), and lipoprotein (a) change was significant compared to the rosiglitazone group (P<0.05). A significant homocysteine decrease was observed in the rosiglitazone group at the end of the study (P<0.05).<br><br>Secondary:<br>After nine and 12 months, mean FPG and PPG levels decreased in both groups compared to baseline (both P<0.05 and P<0.01, respectively).<br><br>HOMA index improved in both groups at 12 months (P<0.05). |
| Berneis et al.[43] (2008)<br><br>Pioglitazone 30 mg QD for 4 weeks, then 45 mg | RCT, XO<br><br>Patients with type 2 diabetes for ≥6 months with a stable $HbA_{1c}$ (6.5 to 9.0%) | N=9<br><br>24 weeks of active treatment (plus an additional 8 | Primary:<br>Change in $HbA_{1c}$, insulin sensitivity, lipid parameters<br><br>Secondary: | Primary:<br>The mean change in $HbA_{1c}$ from baseline to week 12 was -0.54% with pioglitazone and -0.59% with rosiglitazone (P=0.55).<br><br>Insulin resistance decreased 14% with pioglitazone and 10% with rosiglitazone (P=0.51). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| QD for 8 weeks<br><br>vs<br><br>rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks<br><br>All lipid-lowering medications were discontinued 4 weeks prior to the study. | and on a maximum of 2 oral antidiabetic drugs | week wash-out period) | Not reported | There were no significant differences among the treatment groups in the following fasting lipid parameters: HDL-C (P=0.26), LDL-C (P=0.31), LDL size (P=0.51). TC increased more after rosiglitazone compared to pioglitazone (9 vs 3%; P=0.04). TG decreased after treatment with pioglitazone and increased after treatment with rosiglitazone (-21 vs 19%; P=0.004).<br><br>The only postprandial lipid parameters that demonstrated a significant effect of pioglitazone compared to rosiglitazone was an increased LDL-IIB (5 vs -4%; P=□0.01) and decreased LDL-IVB (-15 vs 10%; P=□0.05) after three hours. After six hours, there were no significant changes found.<br><br>Secondary:<br>Not reported |
| Chappuis et al.[44] (2007)<br><br>Pioglitazone 30 mg QD for 4 weeks, then 45 mg QD for 8 weeks<br><br>vs<br><br>rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks<br><br>All lipid-lowering medications were discontinued 4 weeks prior to the study. | RCT, XO<br><br>Patients with type 2 diabetes for ≥6 months with a stable $HbA_{1c}$ (6.5 to 9.0%) and on a maximum of 2 oral antidiabetic drugs | N=17<br><br>24 weeks of active treatment (plus an additional 8 week wash-out period) | Primary:<br>Change in $HbA_{1c}$, FPG, insulin, insulin sensitivity, non-esterified fatty acids, lipid parameters<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with pioglitazone and rosiglitazone resulted in similar changes in $HbA_{1c}$ (-0.3 and -0.5%, respectively; P=0.43), FPG (-1.4 and -1.6 mmol/L, respectively; P=0.68), fasting insulin concentrations (-3.9 and -8.2 mU/L, respectively; P=0.33), insulin sensitivity (-2.4 and -4.7 mmol/L × mU/L, respectively; P=0.33), and fasting non-esterfied fatty acids concentrations (0.2 and -0.5 mmol/L; P=0.25).<br><br>Pioglitazone led to a reduction in fasting TG compared to an increase with rosiglitazone (−0.35 and 0.44 mmol/L, respectively; P=0.037).<br><br>Pioglitazone did not change the fasting TC concentration, whereas there was an increase with rosiglitazone (0.06 and 0.59 mmol/L, respectively; P=0.031).<br><br>Pioglitazone did not change the fasting VLDL-protein concentrations within the VLDL fractions, whereas rosiglitazone increased the protein content of VLDL-2 (−2.6 and 17.7 mg/dL, respectively; P=0.035).<br><br>There were no significant differences on apoB and apoA-I between the groups. Pioglitazone led to a reduction in apoC-II concentrations compared to an increase with rosiglitazone (−0.1 and 1.0 mg/dL, |

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| | | | | respectively; P=0.022). There was no significant difference in apoC-III (P=0.094) or the apoC-II/apoC-III ratio among the groups.<br><br>There was no difference in lipoprotein and hepatic lipase activity among patients receiving pioglitazone and rosiglitazone. Cholesterol ester transfer protein activity decreased after treatment with rosiglitazone and increased following treatment with pioglitazone (−6.2 and 4.6 pmol/mL/min, respectively; P<0.001).<br><br>There was no difference in PPG and post-prandial insulin concentrations between the treatment groups (P=0.944 and P=0.703, respectively). AUC of TG concentrations showed a significant difference between rosiglitazone and pioglitazone (P=0.017). AUC of non-esterfied fatty acids concentrations was not significantly different among the treatment groups (P=0.610).<br><br>The VLDL composition after three and six hours was significantly different following treatment with pioglitazone compared to rosiglitazone, favor of pioglitazone.<br><br>Secondary:<br>Not reported |
| Pavo et al.[45] (2003)<br><br>Pioglitazone 30 to 45 mg daily<br><br>vs<br><br>metformin 850 to 2,550 mg daily | DB, MC, RCT<br><br>Recently diagnosed (<12 months) type 2 diabetic patients ≥40 years old, $HbA_{1c}$ 7.5 to 11.0%, and naïve to oral antihyperglycemic medications | N=205<br><br>32 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline<br><br>Secondary:<br>Changes in FPG, fasting serum insulin, and insulin sensitivity | Primary:<br>Each treatment group had a significant reduction in $HbA_{1c}$ from baseline (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.280).<br><br>Secondary:<br>Each treatment group had a significant reduction in FPG (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.620).<br><br>Pioglitazone reduced fasting serum insulin significantly (P<0.0001). The change in fasting serum insulin was not significant for metformin (P=0.803). Pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of HOMA-S (P=0.002). |

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| Giles et al.[46] (2008)<br><br>Pioglitazone 30 to 45 mg QD<br><br>vs<br><br>glyburide 10 to 15 mg daily<br><br>Insulin was the only rescue medication allowed. | DB, MC, RCT<br><br>Patients ≥18 years of age with type 2 diabetes, $HbA_{1c}$ ≥7.0%, BMI ≤48 kg/m$^2$, NYHA functional Class II/III heart failure, left ventricular systolic dysfunction (≤40%), and receiving sulfonylurea therapy (+/- insulin) for ≥30 days before screening or discontinued metformin therapy within 30 days of screening | N=518<br><br>6 months | Primary:<br>Heart failure progression (defined as the composite of cardiovascular mortality and hospitalization or emergency room visit for heart failure) and metabolic parameters.<br><br>Secondary:<br>Not reported | Primary:<br>Pioglitazone was associated with a higher incidence rate of the composite end point compared with glyburide (13.4 vs 8.2%, respectively; P=0.024).<br><br>Death from cardiovascular cause was similar between the treatment groups (1.9 and 2.3% for pioglitazone and glyburide, respectively).<br><br>Overnight hospitalization for heart failure was higher in the pioglitazone group (9.9%) compared to glyburide group (4.7%).<br><br>Emergency room visits for heart failure occurred in 1.5% of pioglitazone patients compared to 1.2% of glyburide patients.<br><br>Echocardiographic data demonstrated preserved cardiac function with similar changes in the left ventricular mass index (P=0.959) and left ventricular ejection fraction (P=0.413) among the treatment groups. Cardiac index was significantly increased with pioglitazone compared with glyburide (P=0.012).<br><br>FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment. By week 16, a significant difference in mean FPG was observed favoring pioglitazone. At week 24, pioglitazone decreased the $HbA_{1c}$ by -0.98% compared to -0.73% with glyburide (P=0.007).<br><br>At week 24, significant differences were seen between pioglitazone and glyburide in TGs (-36.8 vs +7.6 mg/dL, respectively; P<0.001), HDL-C (+4.8 vs -0.8 mg/dL, respectively; P<.001), and LDL-C (+6.9 vs -2.4 mg/dL, respectively; P<0.016).<br><br>Rates of adverse events and serious adverse events were similar between treatment groups. Hypoglycemia was more common with glyburide and edema was more common with pioglitazone. Weight gain was reported as an adverse event more frequently with pioglitazone than glyburide. (6.1 vs 2.7%, respectively). Mean weight gain was greater (2.10 vs 1.23 kg, respectively; P=0.012) with pioglitazone than with glyburide. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Secondary:<br>Not reported |
| Kahn et al.[47] (2006)<br><br>Rosiglitazone 4 mg QD to 4 mg BID<br><br>vs<br><br>glyburide 2.5 mg QD to 7.5 mg BID<br><br>vs<br><br>metformin 500 mg QD to 1 g BID | DB, MC, RCT (ADOPT)<br><br>Patients 30 to 75 years of age recently diagnosed with type 2 diabetes with a FPG 126 to 180 mg/dL | N=4,360<br><br>4 years | Primary:<br>Time to monotherapy failure (defined as FPG >180 mg/dL after an overnight fast on consecutive testing after at least six weeks of treatment at the maximum-dictated or tolerated dose of study drug)<br><br>Secondary:<br>Effect on FPG, $HbA_{1c}$, weight, insulin sensitivity, β-cell function, adverse events | Primary:<br>The cumulative incidence of monotherapy failure at five years was 15% for rosiglitazone, 34% for glyburide and 21% with metformin. This represents a risk reduction of 63% for rosiglitazone as compared with glyburide, and 32% for rosiglitazone as compared with metformin (P<0.001 for both comparisons).<br><br>Secondary:<br>The rate of progression to a confirmed FPG >140 mg/dL was significantly lower with rosiglitazone than glyburide (RR, 62%; 95% CI, 51 to 72; P<0.001) or metformin (RR, 36%; 95% CI, 15 to 52; P=0.002).<br><br>At the four-year evaluation, 40% of the patients in the rosiglitazone group had an $HbA_{1c}$ <7.0%, as compared with 26% for glyburide (P<0.001) and 36% for metformin (P=0.03).<br><br>Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide (P<0.001 for all comparisons).<br><br>During the first six months, insulin sensitivity increased more in the rosiglitazone group than in the metformin group. Thereafter, insulin sensitivity improved at similar rates in the two groups, with a significant difference between the two groups noted at four years (P<0.001). Insulin sensitivity did not change significantly in the glyburide group.<br><br>During the first six months, levels of β-cell function increased more with glyburide than rosiglitazone or metformin. Thereafter, levels of β-cell function declined in all three groups. The annual rate of decline after six months was 6.1% for glyburide (P<0.001), 3.1% for metformin (P=0.02) and 2.0% for rosiglitazone.<br><br>The number of deaths from all causes was similar in the three groups; however, adverse events differed among the groups. |

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| | | | | Glyburide was associated with a lower risk of cardiovascular events (MI, CHF and stroke) than was rosiglitazone (P<0.05), and the risk associated with metformin was similar to that with rosiglitazone. There was no significant difference in the risk for CHF with rosiglitazone compared to metformin (HR, 1.22; 95% CI, 0.66 to 2.26; P=0.52), but the risk was significantly higher with rosiglitazone than glyburide (HR, 2.20; 95% CI, 1.01 to 4.79; P=0.05).<br><br>While there was no significant difference noted in men, significantly more women who received rosiglitazone (9.30%) than glyburide (3.47%) or metformin (5.08%) experienced fractures (both P<0.01). |
| Russell-Jones et al.[48] (2012) DRUATION-4<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>metformin 2,000 mg/day<br><br>vs<br><br>pioglitazone 45 mg/day<br><br>vs<br><br>sitagliptin 100 mg/day | DB, DD, MC, PG, RCT<br><br>Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with $HbA_{1c}$ 7.1 to 11.0%, BMI 23 to 45 kg/m$^2$, and stable weight | N=820<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported quality of life | Primary:<br>Decreases in $HbA_{1c}$ were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The $HbA_{1c}$ at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively.<br><br>Secondary:<br>Similar proportions of patients receiving exenatide ER and metformin achieved $HbA_{1c}$ <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved $HbA_{1c}$ <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001).<br><br>Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26).<br><br>Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar |

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| | | | | among all treatments.<br><br>Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892).<br><br>No clinically significant changes in serum lipids were observed with any treatment.<br><br>Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329).<br><br>Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment.<br><br>All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER |

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| | | | | compared to pioglitazone (P values not reported). |
| Nichols et al.[49] (2007)<br><br>Metformin<br><br>vs<br><br>sulfonylurea<br><br>vs<br><br>insulin<br><br>vs<br><br>TZDs | MC, OS, RETRO<br><br>Patients who initiated metformin, sulfonylurea, insulin or TZDs between 1996 and 2002 and continued use of that drug for at least 12 months without adding other therapies | N=9,546<br><br>≥12 months | Primary:<br>Weight changes<br><br>Secondary:<br>Not reported | Primary:<br>Patients treated with metformin lost an average of 2.4 kg, sulfonylurea-treated patients gained 1.8 kg, insulin-treated patients gained 3.3 kg, and thiazolidinedione-treated patients gained 5.0 kg. All comparisons with metformin were statistically significant.<br><br>Secondary:<br>Not reported |
| Norris et al.[50] (2007)<br><br>Pioglitazone<br><br>vs<br><br>rosiglitazone | MA (112 trials)<br><br>Patients with metabolic syndrome, pre-diabetes, and type 2 diabetes receiving treatment with pioglitazone or rosiglitazone | N=14,290<br><br>Duration varied | Primary:<br>$HbA_{1c}$, lipids, weight, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>For pioglitazone, the between-group change in $HbA_{1c}$ was -0.99% (95% CI, -1.18 to -0.81) and for rosiglitazone was -0.92% (95% CI, -1.2 to -0.64). Indirect comparison of pioglitazone and rosiglitazone found no significant difference in $HbA_{1c}$ (between-group difference, -0.07%; 95% CI, -0.41 to 0.27).<br><br>Rosiglitazone increased TC (13.70 mg/dL; 95% CI, 1.06 to 26.35) and pioglitazone decreased TG levels (-1.08 mg/dL; 95% CI, -2.08 to -0.09). Using indirect comparisons, rosiglitazone increased TC compared to pioglitazone (net between-drug effect, 13.91 mg/dL; 95% CI, 1.20 to 26.62).<br><br>Data were insufficient to assess comparative effects of pioglitazone and rosiglitazone on microvascular and macrovascular events. Few data were available on the comparative effect of pioglitazone and rosiglitazone on cardiovascular risk factors among persons with pre-diabetes or the metabolic syndrome. There were insufficient data to determine whether pioglitazone and rosiglitazone have different effects on the incidence of diabetes among persons with either pre-diabetes or the metabolic |

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| | | | | syndrome.<br><br>There was limited reporting of adverse events in the available head-to-head trials. Among 719 patients with type 2 diabetes and dyslipidemia, there were no differences between pioglitazone and rosiglitazone at 24-weeks follow-up for weight change (pioglitazone, 2.0 kg and rosiglitazone, 1.6 kg; P=0.164), liver function tests, creatinine phosphokinase, BP, heart rate, hematocrit, hypoglycemic episodes, edema, or congestive heart failure.<br><br>There were generally no differences in rates of adverse events between the active-treatment and placebo groups. The most frequently reported adverse events were edema, hypoglycemia, and weight gain. Both drugs increased weight compared to placebo: pioglitazone, 2.96 kg (95% CI, 0.73 to 5.20) and rosiglitazone, 2.12 kg (95% CI, 0.89 to 3.36), with no significant difference between the two drugs (95% CI, -1.71 to 3.39).<br><br>Secondary:<br>Not reported |
| Singh et al.[51] (2011)<br><br>TZDs (pioglitazone, rosiglitazone)<br><br>vs<br><br>placebo, sulfonylurea, or metformin | MA, SR (13 RCTs)<br><br>Type 2 diabetics | N=17,627<br><br>1 to 5.5 years (follow-up) | Primary:<br>Any pneumonia or lower respiratory tract infection reported as an adverse event, pneumonia or lower respiratory tract infection reported as a serious adverse event<br><br>Secondary:<br>Not reported | Primary:<br>TZDs are associated with a significantly increased risk for any pneumonia or lower respiratory tract infection compared to control (130/8,163 vs 100/9,464; RR, 1.40; 95% CI, 1.08 to 1.82; P=0.01). In addition TZDs were associated with a significantly increased risk of serious pneumonia or lower respiratory tract infection compared to control (111/7,391 vs 87/8,692; RR, 1.39; 95% CI, 1.05 to 1.83; P=0.02).<br><br>Secondary:<br>Not reported |
| Loke et al.[52] (2009) | MA (2 OS, 10 RCTs) | N=45,394<br><br>≥1 years | Primary:<br>Incidence of fracture, change in | Primary:<br>Rosiglitazone and pioglitazone were associated with a significantly increased risk of fractures overall in the 10 RCTs (OR, 1.45; 95% CI, 1.18 |

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| TZDs (rosiglitazone, pioglitazone, troglitazone*)<br><br>vs<br><br>no TZDs | Type 2 diabetics with impaired glucose | | baseline BMD<br><br>Secondary:<br>Not reported | to 1.79; *P*<0.001). Five of these RCTs demonstrated a significantly increased risk of fractures among women (OR, 2.23; 95% CI, 1.65 to 3.01; *P*<0.001), but not among men (OR, 1.00; 95% CI, 0.73 to 1.39; *P*=0.98). The two OS demonstrated an increased risk of fractures with rosiglitazone and pioglitazone.<br><br>BMD at the lumbar spine (WMD, -1.11%; 95% CI, -2.08 to -0.14; *P*=0.02) and hip (WMD, -1.24%; 95% CI, -2.34 to -0.67; *P*<0.001) significantly decreased in women receiving TZDs within two RCTs. Results from one OS supported these findings (WMD, -1.36%; 95% CI, -2.05 to -0.67; *P*=0.001 and WMD, -1.24%; 95% CI, -1.78 to -0.70; *P*<0.001).<br><br>Secondary:<br>Not reported |
| Louisa et al.[53] (2011)<br><br>TZDs (pioglitazone, rosiglitazone)<br><br>vs<br><br>placebo or other hypoglycemic agents | MA (37 RCTs)<br><br>Type 2 diabetics | N=3,000<br><br>>3 months | Primary:<br>Glycemic outcomes<br><br>Secondary:<br>Change in baseline BMI, lipid profile, BP, high-sensitivity CRP, and insulin sensitizing effect; cardiovascular and clinical endpoints | Primary:<br>Both pioglitazone (WMD, -0.12%; 95% CI, -0.38 to -0.16) and rosiglitazone (WMD, -0.47%; 95% CI, -0.62 to -0.33) significantly decreased $HbA_{1c}$. Pioglitazone only demonstrated a significant decrease compared to placebo, while rosiglitazone significantly decreased $HbA_{1c}$ compared to placebo and a sulfonylurea.<br><br>Both pioglitazone (WMD, -9.16 mg/dL; 95% CI, -15.60 to -2.72) and rosiglitazone (WMD, -16.10 mg/dL; 95% CI, -22.20 to -10.01) significantly decreased FPG compared to control. Pioglitazone demonstrated a significant decrease compared to placebo, metformin, and voglibose*, while rosiglitazone significantly decreased FPG compared to placebo, metformin, and a sulfonylurea.<br><br>Secondary:<br>Pioglitazone and rosiglitazone had similar effects on BMI (pioglitazone: WMD, 0.57; 95% CI, 0.34 to 0.80 and rosiglitazone: WMD, 0.72; 95% CI, 0.29 to 1.14).<br><br>Pioglitazone demonstrated a neutral effect of LDL-C (WMD, 3.89 mg/dL; 95% CI, -0.04 to 7.83) and TC (WMD, 2.30 mg/dL; 95% CI, -3.81 to 8.41). |

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| | | | | Rosiglitazone significantly increased LDL-C (WMD, 11.30 mg/dL; 95% CI, 7.80 to 14.79) and TC (WMD, 7.34 mg/dL; 95% CI, 2.34 to 12.31). Both agents had favorable effects on HDL-C and TGs.<br><br>Pioglitazone produced a small decrease in DBP and SBP, while rosiglitazone demonstrated a neutral effect.<br><br>In 13 trials, pioglitazone demonstrated a neutral effect on high sensitivity CRP, while rosiglitazone demonstrated a small improvement in hsCRP.<br><br>Consistent increase in adiponectin and improvement in HOMA-IR were observed with both pioglitazone and rosiglitazone.<br><br>Four trials evaluated cardiovascular events as secondary endpoints. There were significant decreases in major cardiac events with both pioglitazone vs control (RR, 0.24; 95% CI, 0.09 to 0.63) and rosiglitazone vs control (RR, 0.41; 95% CI, 0.19 to 0.87). |
| Bolen et al.[54] (2007)<br><br>Biguanides<br><br>vs<br><br>meglitinides<br><br>vs<br><br>TZDs<br><br>vs<br><br>α-glucosidase inhibitors<br><br>vs | MA (Analysis of 216 controlled trials and cohort studies, and 2 SRs)<br><br>Patients with type 2 diabetes | N=136 (articles on intermediate outcomes)<br><br>N=167 (articles on adverse events)<br><br>N=68 (articles on microvascular outcomes and mortality)<br><br>Duration varied | Primary:<br>Intermediate outcomes: $HbA_{1c}$, body weight, BP, lipid panels, all-cause mortality, cardiovascular morbidity and mortality, microvascular outcomes<br><br>Secondary:<br>Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or | Primary:<br>Results from clinical trials showed that most oral agents including TZDs, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in $HbA_{1c}$ level of about 1%). Nateglinide and α-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials.<br><br>TZDs were the only class with beneficial effect on HDL-C (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL-C (mean relative increase, 10 mg/dL) compared to other oral agents. Metformin decreased LDL-C levels by about 10 mg/dL, whereas other oral agents had no effects on LDL-C.<br><br>TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on SBP.<br><br>Most agents except metformin increased body weight by 1 to 5 kg.<br><br>In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of |

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| second-generation sulfonylureas | | | hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization, other serious adverse events | cardiovascular events was lower with glyburide compared to rosiglitazone or metformin (1.8, 3.4, and 3.2%, respectively; P<0.05).<br><br>In the RECORD study (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes), rosiglitazone plus metformin or a sulfonylurea compared to metformin plus a sulfonylurea had a HR of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The HR was driven by more congestive heart failure in the rosiglitazone plus metformin group compared to the control group of metformin plus sulfonylurea (absolute risk, 1.7 vs 0.8%, respectively).<br><br>Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes.<br><br>Secondary:<br>According to several RCTs and some OS trials, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many RCTs, TZDs were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2 to 21%).<br><br>In cohort studies, TZDs were associated with higher risk for congestive heart failure although absolute risks were small (1 to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared to sulfonylureas and metformin.<br><br>In many trials and a few OS trials, metformin was associated with greater risk for gastrointestinal problems compared to other oral diabetes agents.<br><br>According to a SR of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents. |
| Monami et al.[55] (2008)<br><br>Metformin<br><br>vs | MA<br><br>Patients with type 2 diabetes mellitus | N=7,890 (27 RCT)<br><br>Variable duration | Primary:<br>Reduction in $HbA_{1c}$ at 16 to 36 months<br><br>Secondary: | Primary:<br>Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in $HbA_{1c}$ by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. |

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| sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists | | | Not reported | In direct comparisons, sulfonylureas led to a greater reduction in $HbA_{1c}$ (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.<br><br>Secondary:<br>Not reported |
| Shyangdan et al.[56] (2011)<br><br>GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)<br><br>vs<br><br>non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas) | MA (RCTs)<br><br>Type 2 diabetics ≥18 years of age | N=not reported<br><br>8 to 26 weeks | Primary:<br>Change in baseline $HbA_{1c}$, incidence of hypoglycemia, weight change<br><br>Secondary:<br>Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function | Primary:<br>Change in baseline $HbA_{1c}$<br>Exenatide ER significantly decreased $HbA_{1c}$ compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an $HbA_{1c}$ <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an $HbA_{1c}$ <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).<br><br>Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased $HbA_{1c}$ (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI, -0.53 to -0.15; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in $HbA_{1c}$ compared to sulfonylureas (-0.01%; 95% CI -0.27 to 0.29; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). |

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| | | | | Compared to placebo, liraglutide 1.8 mg significantly decreased an $HbA_{1c}$ (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve $HbA_{1c}$ <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased $HbA_{1c}$ to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving $HbA_{1c}$ <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in $HbA_{1c}$ compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).<br><br>Liraglutide decreased $HbA_{1c}$ to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an $HbA_{1c}$ <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported).<br><br>Liraglutide 1.2 mg was associated with a non-significant increase in $HbA_{1c}$ compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an $HbA_{1c}$ <7.0% compared to the 1.8 mg dose (P=0.92).<br><br>Incidence of hypoglycemia<br>The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients).<br><br>Overall, there was no difference in the incidence of minor hypoglycemia |

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| | | | | between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001).<br><br>Weight loss<br>Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001).<br><br>Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported).<br><br>Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and sulfonylureas (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported).<br><br>Patients were more likely to experience weight gain with liraglutide 1.2 compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported).<br><br>Secondary:<br>Data on mortality and morbidity were not reported for any treatment. |

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| | | | | Quality of life<br>Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine.<br><br>Data for liraglutide were not reported.<br><br>Safety<br>Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%).<br><br>Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas.<br><br>BP<br>There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. |

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| | | | | Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported.<br><br>FPG<br>There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).<br><br>Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported).<br><br>PPG<br>There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a six-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001).<br><br>Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that |

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| | | | | PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable.<br><br>Lipid profile<br>TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported.<br><br>Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported.<br><br>β cell function<br>Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio. |
| **Type 2 Diabetes – Combination Therapy** | | | | |
| Chogtu et al.[57] (2009)<br><br>Pioglitazone (variable doses) and glimepiride 2 mg daily<br><br>vs<br><br>rosiglitazone (variable doses) and glimepiride 2 mg daily | OL, RCT<br><br>Patients 30 to 70 years of age with type 2 diabetes who received glimepiride and required a TZD due to a lack of glycemic control, normotensive, and not on antilipemic therapy | N=63<br><br>12 weeks | Primary:<br>Blood glucose levels, plasma lipids, BP<br><br>Secondary:<br>Not reported | Primary:<br>The mean change in the FPG and PPG from baseline to week 12 was significant in both groups (P<0.05). There was no significant difference between the groups with regard to the change in FPG (P=0.10) and PPG (P=0.95).<br><br>$HbA_{1c}$ levels also decreased from baseline to week 12. There was no significant difference between the treatment groups (P>0.05).<br><br>At week 12, 37.9% of patients in the pioglitazone group and 17.8% of patients in the rosiglitazone group had $HbA_{1c}$ <7.0% (P value not reported).<br><br>TC decreased in both treatment groups; however, to a greater extent with |

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| | | | | pioglitazone compared to rosiglitazone (P=0.004). TG in the pioglitazone group (P=0.0006) decreased significantly in comparison to the rosiglitazone group (P=0.255) at 12 weeks (P=0.002 pioglitazone vs rosiglitazone). LDL-C decreased significantly (P=0.005) in the pioglitazone group compared to the rosiglitazone group. There was no significant difference in HDL-C among the treatment groups (P>0.05).<br><br>There was no change in SBP with pioglitazone or rosiglitazone from baseline to week 12. There was also no significant difference in SBP between the treatment groups (P=0.45).<br><br>There was an increase in the weight following treatment with pioglitazone and rosiglitazone; however, there was no difference between the groups (P=0.10).<br><br>Secondary:<br>Not reported |
| Brackenridge et al.[58] (2009)<br><br>Pioglitazone 30 mg/day<br><br>vs<br><br>rosiglitazone 8 mg/day<br><br>vs<br><br>placebo<br><br>All patients also received metformin. | DB, PC, RCT<br><br>Type 2 diabetics for ≥6 months currently managed on metformin and diet and exercise | N=24<br><br>3 months | Primary:<br>Change in baseline lipid profile<br><br>Secondary:<br>Change in baseline glycemic outcomes | Primary:<br>Of the various lipid concentrations, pioglitazone only significantly decreased non-esterified fatty acid (0.66±0.08 to 0.48±0.04 mmol/L; P=0.02) and VLDL-TG:apoB (31.00±3.91 to 25.30±3.71; P=0.04) compared to baseline. Rosiglitazone also only significantly decreased non-esterified fatty acid (0.68±0.09 to 0.49±0.10; P=0.003) and VLDL-TG:apoB (25.50±2.70 to 20.60±2.47; P=0.01). Placebo significantly increased LDL-C compared to baseline (2.10±0.10 to 2.50±0.19; P=0.03). No significant differences were observed between any of the treatments.<br><br>Of the various LDL subfraction concentrations, pioglitazone significantly increased LDL3-C compared to placebo (1.25±0.15 to 1.53±0.23 mmol/L; P=0.05). Rosiglitazone significantly increased LDL2-C (1.02±0.14 to 1.39±0.20 mmol/L; P=0.02) and LDL2 apoB (0.25±0.03 to 0.34±0.05 mmol/L; P=0.02), and significantly decreased LDL3-C (1.33±0.12 to 0.96±0.14 mmol/L; P=0.02). Decreases in LDL3-C (P=0.03) and LDL3 apoB (P=0.03) with rosiglitazone were significantly greater compared to pioglitazone.<br><br>Of the various lipoprotein metabolism variables, rosiglitazone only |

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| | | | | decreased VLDL absolute secretion rate compared to baseline (7.24 to 5.83 mg/kg/day; P=0.01). No significant differences were observed between any of the treatments.<br><br>Secondary:<br>Of the glycemic outcomes evaluated, pioglitazone significantly decreased $HbA_{1c}$ (7.50±0.21 to 6.80±0.18; P=0.01) and significantly increased body weight (96.40±3.62 to 98.30±3.96; P=0.04) and BMI (30.80±1.26 to 31.50±1.45; P=0.04) compared to baseline. Rosiglitazone significantly decreased $HbA_{1c}$ compared to baseline (6.90±0.30 to 6.50±0.19; P=0.04). No significant differences were observed between any of the treatments. |
| Einhorn et al.[59] (2000)<br><br>Pioglitazone 30 to 45 mg and metformin (existing therapy)<br><br>vs<br><br>metformin (existing therapy) | DB, PC, RCT<br><br>Patients with poorly controlled type 2 diabetes ($HbA_{1c}$ ≥8.0%) with metformin monotherapy | N=328<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$, FPG, insulin, lipoproteins, and C-peptide<br><br>Secondary:<br>Not reported | Primary:<br>Reductions in $HbA_{1c}$ with pioglitazone add-on therapy were significantly lower compared to placebo (-0.83% difference between treatment groups; P≤0.05).<br><br>Reductions in FPG with pioglitazone add-on therapy were significantly lower compared to placebo (-37.7 mg/dL difference between treatment groups; P≤0.05).<br><br>Pioglitazone reduced fasting C-peptide levels (-0.1 ng/mL) while placebo increased levels (0.1 ng/mL; P≤0.05).<br><br>Pioglitazone reduced fasting C-insulin levels (-2.1 ng/mL) while placebo increased levels (0.4 ng/mL; P<0.05).<br><br>Pioglitazone add-on therapy significantly reduced TG (-9.7 vs 8.5 mg/dL; P≤0.05) and increased HDL-C (10.2 vs 1.5 mg/dL; P≤0.05) compared to placebo.<br><br>Both treatment groups increased LDL-C (7.7 vs 11.9 mg/dL; P value not significant).<br><br>No significant difference between treatment groups in number of adverse events was observed. Higher rate of edema was reported with pioglitazone (5.9 vs 2.5%). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Weight loss was observed with placebo (-1.36 kg) while patients receiving pioglitazone had weight gain (0.95 kg; P value not reported).<br><br>Secondary:<br>Not reported |
| Kaku et al.[60] (2009)<br><br>Pioglitazone 15 to 30 mg QD and metformin 500 to 750 mg daily<br><br>vs<br><br>metformin 500 to 750 mg daily | DB, PC, PG, RCT<br><br>Patients 20 to 65 years of age with type 2 diabetes, $HbA_{1c}$ 6.5 to 10.0%, who were drug naïve or on metformin monotherapy | N=169<br><br>28 weeks | Primary:<br>$HbA_{1c}$, FPG, fasting insulin, insulin resistance, lipid parameters<br><br>Secondary:<br>Not reported | Primary:<br>At week 28, mean change in $HbA_{1c}$ from baseline was -0.67% with pioglitazone compared to 0.25% with placebo (P<0.0001).<br><br>More patients receiving pioglitazone achieved an $HbA_{1c}$ <6.5% compared to placebo (38.6 vs 8.1%, respectively; P<0.0001).<br><br>At week 28, mean change in FPG from baseline was -20.5 mg/dL with pioglitazone compared to 1.9 mg/dL with placebo (P<0.0001).<br><br>Mean fasting insulin concentrations were reduced to a greater extent with pioglitazone (-2.15 mU/mL) compared to placebo (-0.38 mU/mL; P=0.021).<br><br>Insulin resistance was reduced more by pioglitazone compared to placebo (-1.34 vs -0.15; P=0.0025).<br><br>The main differences in lipids between pioglitazone compared to placebo were significant increases in TC (P=0.0057) and HDL-C (P<0.0001). Adiponectin levels were significantly increased by pioglitazone compared to placebo (P=0.0001).<br><br>Secondary:<br>Not reported |
| Perez et al.[61] (2009)<br><br>Pioglitazone/ metformin fixed dose combination 15/850 mg BID | DB, PG, RCT<br><br>Patients ≥18 years of age with type 2 diabetes, $HbA_{1c}$ 7.5 to 10.0%, BMI ≤45 $kg/m^2$, who were drug naïve | N=600<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>$HbA_{1c}$ responder rate, changes in baseline FPG, | Primary:<br>At week 24, mean change in $HbA_{1c}$ from baseline was -1.83% with pioglitazone/metformin compared to -0.96% pioglitazone and -0.99% with metformin (P<0.0001 for combination therapy vs either monotherapy).<br><br>Secondary:<br>In the pioglitazone/metformin group, 63.8% achieved $HbA_{1c}$ <7.0% compared to 46.9% with pioglitazone and 38.9% with metformin (P value |

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| vs<br><br>pioglitazone 15 mg BID<br><br>vs<br><br>metformin 850 mg BID | | | fasting insulin, insulin resistance | not reported).<br><br>Pioglitazone/metformin led to the greatest reduction in FPG from baseline to final visit (-39.9 mg/dL) compared to -22.2 mg/dL with pioglitazone and -24.8 mg/dL with metformin (P<0.01 for combination therapy vs either monotherapy).<br><br>Pioglitazone/metformin led to the greatest reduction in fasting insulin from baseline to final visit (-3.91 µIU/mL), followed by pioglitazone (-3.18 µIU/mL). Both reductions were significantly greater compared to metformin (-0.98 µIU/mL; P<0.05).<br><br>At week 24, the greatest decrease in insulin resistance was seen with pioglitazone/metformin and pioglitazone compared to metformin; however, the difference was significant only with pioglitazone/metformin (P<0.01). |
| Kipnes et al.[62] (2001)<br><br>Pioglitazone 15 to 30 mg<br><br>vs<br><br>plus<br><br>All patients received existing sulfonylurea regimens. | DB, MC, PC, RCT<br><br>Patients on a stable regimen of a sulfonylurea for ≥30 days with an $HbA_{1c}$ ≥8.0%, fasting C-peptide >1 ng/mL, BMI 25 to 45 kg/m$^2$ | N=560<br><br>16 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, TG, and lipoproteins<br><br>Secondary:<br>Not reported | Primary:<br>Patients receiving pioglitazone and a sulfonylurea had significant decreases (P<0.05) from baseline in $HbA_{1c}$ and FPG levels compared to patients in the placebo and sulfonylurea group.<br><br>Both pioglitazone and sulfonylurea groups had significant (P<0.05) mean percent decreases in TG levels (-17%; 95% CI, -6 to -27 for 15 mg and -26%; 95% CI, -16 to -36 for 30 mg) and increases in HDL-C levels (6%; 95% CI, 1 to 11 for 15 mg and 13%; 95% CI, 8 to 18 for 30 mg) compared to the placebo and sulfonylurea group.<br><br>There were small but statistically significant (P≤0.05) mean percent increases in LDL-C levels in all groups.<br><br>The adverse event rates were similar in all groups.<br><br>Secondary:<br>Not reported |
| Matthews et al.[63] (2005) | DB, RCT<br><br>Patients with type 2 | N=630<br><br>12 months | Primary:<br>Effect on $HbA_{1c}$ | Primary:<br>Similar reductions in $HbA_{1c}$ were observed in pioglitazone- (–0.99%) and gliclazide-treated groups (–1.01%; P=0.837). |

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| Pioglitazone 15 to 45 mg QD and metformin (existing therapy)<br><br>vs<br><br>gliclazide* 80 to 320 mg QD and metformin (existing therapy) | diabetes that was poorly controlled ($HbA_{1c}$ 7.5 to 11.0%) with metformin monotherapy | | Secondary:<br>Effect on FPG, insulin, lipoproteins, and C-peptide | Secondary:<br>Similar reductions in FPG were observed in pioglitazone- (–2.1 mmol/L) and gliclazide- (–1.6 mmol/L) treated groups (P=0.506).<br><br>Gliclazide significantly reduced LDL-C compared to pioglitazone (–4.2 vs +10.4 mg/dL; P=0.001).<br><br>Pioglitazone significantly reduced TG (–53.1 vs –19.5 mg/dL; P<0.001) and increased HDL cholesterol (6.9 mg/dL vs no change; P<0.001) compared to gliclazide. |
| Charbonnel et al.[64] (2005)<br><br>Pioglitazone 15 to 45 mg QD and metformin (existing therapy)<br><br>vs<br><br>gliclazide* 80 to 320 mg QD and metformin (existing therapy) | DB, RCT<br><br>Patients with type 2 diabetes that was poorly controlled ($HbA_{1c}$ 7.5 to 11.0%) with metformin monotherapy | N=630<br><br>24 months | Primary:<br>Effect on $HbA_{1c}$<br><br>Secondary:<br>Effect on FPG, insulin, lipoproteins, and C-peptide | Primary:<br>Similar reductions in $HbA_{1c}$ were observed with pioglitazone add-on therapy (–0.89%) and with gliclazide add-on therapy (–0.77%; P=0.200) after two years.<br><br>Secondary:<br>Significant reductions in FPG were observed with pioglitazone add-on therapy (–1.8 mmol/L) compared to gliclazide add-on therapy (–1.1 mmol/L; P<0.001) after two years.<br><br>Gliclazide add-on therapy had significantly reduced LDL-C compared to pioglitazone add-on therapy (–6 vs +2 mg/dL; P<0.001).<br><br>Pioglitazone add-on therapy significantly reduced TG (–23 vs –7 mg/dL; P<0.001) and increased HDL-C (22 vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy.<br><br>No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported.<br><br>Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg). |
| Hanefeld et al.[65] (2004)<br><br>Pioglitazone 15 to | DB, MC, PG, RCT<br><br>Patients with type 2 diabetes | N=639<br><br>12 months | Primary:<br>Change in $HbA_{1c}$<br><br>Secondary: | Primary:<br>$HbA_{1c}$ was reduced by 1.20 and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments). |

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| 45 mg QD and sulfonylurea (existing therapy)<br><br>vs<br><br>metformin 850 to 2,250 mg daily and sulfonylurea (existing therapy) | inadequately controlled on sulfonylurea monotherapy | | FPG, fasting plasma insulin, lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio) | Secondary:<br>FPG (P=0.528) and fasting plasma insulin (P=0.199) were also reduced but the between-treatment differences were not statistically significant.<br><br>Pioglitazone addition to sulfonylurea significantly reduced TG (–16 vs –9%; P=0.008) and increased HDL-C (14 vs 8%; P<0.001) compared with metformin addition.<br><br>LDL-C was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001).<br><br>Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017). Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group. |
| Comaschi et al.[66] (2008)<br><br>Pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea)<br><br>vs<br><br>metformin/ glibenclamide‡ fixed dose combination 400/2.5 mg<br>1 to 3 tablets daily | MC, OL, PG, RCT<br><br>Patients ≥35 years of age with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months before study entry, $HbA_{1c}$ 7.5 to 11.0%, and fasting C-peptide >0.33 nmol/L | N=250<br><br>6 months | Primary:<br>Change in $HbA_{1c}$ from baseline to six months<br><br>Secondary:<br>Change in lipid profiles after six months of treatment | Primary:<br>Pioglitazone-based and fixed-dose metformin/glibenclamide resulted in similar reductions in $HbA_{1c}$ (-1.11 vs -1.29%, respectively; P=0.192) and FPG (-2.13 vs -1.81 mmol/L, respectively; P=0.370).<br><br>Secondary:<br>No changes in TC were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479).<br><br>The addition of pioglitazone to metformin or a sulfonylurea led to a slight increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001).<br><br>There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677).<br><br>There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425) |

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| | | | | There was a significant reduction in TGs with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045). |
| Seufert et al.[67] (2008)<br><br>Study 1<br>Pioglitazone 15 to 45 mg QD and metformin (existing therapy)<br><br>vs<br><br>gliclazide* 80 to 320 mg daily and metformin (existing therapy)<br><br>Study 2<br>Pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy)<br><br>vs<br><br>metformin 850 to 2,550 mg daily and sulfonylurea (existing therapy) | 2 MC, RCT<br><br>Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy ($HbA_{1c}$ 7.5 to 11.0%), and fasting C-peptide >1.5 ng/ml) | N=1,269<br><br>104 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline, FPG, glucose excursions using Three hour oral glucose tolerance test, and insulin sensitivity<br><br>Secondary:<br>Not reported | Primary:<br>Study 1<br>The mean change in $HbA_{1c}$ from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20).<br><br>The mean change in FPG from baseline to week 104 was -1.8 mmol/l with pioglitazone and metformin compared to -1.1 mmol/l with gliclazide and metformin (P<0.001).<br><br>Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the two-year treatment period. This effect was not seen in the patients receiving gliclazide for two years as add-on therapy to failing metformin.<br><br>Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001).<br><br>Study 2<br>The mean change in $HbA_{1c}$ from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173).<br><br>The mean change in FPG from baseline to week 104 was -2.0 mmol/L with pioglitazone and sulfonylurea compared to -1.9 mmol/L with metformin and sulfonylurea (P=0.506).<br><br>The addition of pioglitazone to failing sulfonylurea therapy for two years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment.<br><br>Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to |

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| | | | | sulfonylurea (P=0.581 between treatments).<br><br>Secondary:<br>Not reported |
| Bergenstal et al.[68] (2010) DURATION-2<br><br>Exenatide ER 2 mg SC once weekly<br><br>vs<br><br>sitagliptin 100 mg QD<br><br>vs<br><br>pioglitazone 45 mg QD<br><br>All patients received existing metformin therapy. | DB, DD, MC, PG, RCT<br><br>Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, $HbA_{1c}$ 7.1 to 11.0%, and BMI 25 to 45 $kg/m^2$ | N=514<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving an $HbA_{1c}$ ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety | Primary:<br>Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased $HbA_{1c}$ compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165).<br><br>Secondary:<br>A significantly greater proportion of patients receiving exenatide achieved $HbA_{1c}$ targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone.<br><br>Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024).<br><br>In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported).<br><br>Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001).<br><br>Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, |

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| | | | | 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0).<br><br>Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001).<br><br>Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only).<br><br>All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported).<br><br>All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406).<br><br>The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported. |
| Aljabri et al.[69] | OL, RCT | N=62 | Primary: | Primary: |

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| (2004)<br><br>Pioglitazone 30 to 45 mg QD<br><br>vs<br><br>NPH insulin 0.3 unit/kg QD<br><br>All patients were receiving existing sulfonylurea or metformin therapy. | Patients with poorly controlled type 2 diabetes ($HbA_{1c}$ >8.0%) with insulin secretagogues and metformin monotherapy | 16 weeks | Effect on $HbA_{1c}$, FPG, incidence of hypoglycemia (<68 mg/dL), effect on lipoproteins, quality of life (assessed using the DTSQ)<br><br>Secondary:<br>Not reported | Similar reductions in $HbA_{1c}$ were observed in pioglitazone-treated (–1.9%) and NPH insulin-treated patients (–2.3%; P=0.32).<br><br>Nonsignificant differences in reduction in FPG were observed with NPH insulin (–77 mg/dL) and pioglitazone (–52 mg/dL; P=0.07).<br><br>Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02).<br><br>Significant increases in HDL-C were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02).<br><br>No significant differences in TC, LDL-C and TG were reported between the two treatment groups.<br><br>No significant differences were noted for the DTSQ scores between the two treatment groups.<br><br>Secondary:<br>Not reported |
| Dorkhan et al.[70] (2008)<br><br>Pioglitazone 30 to 45 mg QD and existing oral hypoglycemic therapy<br><br>vs<br><br>insulin glargine 6 to 10 IU/day administered in the morning (titrated as necessary) and existing oral | RCT, OL<br><br>Patients with type 2 diabetes and inadequate glycemic control (defined as treatment with metformin and sulfonylurea/ meglitinide in doses ≥50% of maximum recommended doses and $HbA_{1c}$ >6.2% | N=36<br><br>26 weeks | Primary:<br>Change in $HbA_{1c}$, β-cell function, insulin sensitivity, degree of patient satisfaction<br><br>Secondary:<br>Not reported | Primary:<br>After 26 weeks, the change in $HbA_{1c}$ from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050).<br><br>There was no difference in insulin, β-cell function, or insulin sensitivity among the two treatment groups (P=NS). Insulin glargine resulted in a greater reduction in proinsulin concentrations than pioglitazone (-55% vs -25%; P<0.01).<br><br>Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P=NS).<br><br>The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups. |

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| hypoglycemic therapy | | | | There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups).<br><br>Secondary:<br>Not reported |
| Ligvay et al.[71] (2009)<br><br>Pioglitazone 15 to 45 mg QD plus glyburide 1.25 mg BID<br><br>vs<br><br>insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily All patients were receiving metformin 1,000 mg BID<br><br>Doses of medications could be titrated at the investigator's discretion. | RCT, OL<br><br>Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve | N=58<br><br>36 months | Primary:<br>$HbA_{1c}$, rate of treatment failures (defined as $HbA_{1c}$ >8.0%), hypoglycemia, weight gain, compliance, QoL, and patient satisfaction<br><br>Secondary:<br>Not reported | Primary:<br>After 36 months, $HbA_{1c}$ was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26).<br><br>The percentage of patients achieving $HbA_{1c}$ <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the $HbA_{1c}$ goal at the end of 36 months.<br><br>Three patients in each group reached the "treatment failure" end point.<br><br>The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53).<br><br>In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) vs 3.36 kg (-0.47 to 7.20; P=0.04).<br><br>Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group.<br><br>There were differences between the groups for any of the 12 QoL domains evaluated.<br><br>All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization.<br><br>Secondary: |

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| | | | | Not reported |
| Meneghini et al (abstract).[72] (2010)<br><br>Insulin glargine<br><br>vs<br><br>pioglitazone | MC, OL, PG<br><br>Adults with poorly controlled type 2 diabetes ($HbA_{1c}$ 8.0 to 12.0%), despite ≥3 months of sulfonylurea or metformin monotherapy | N=389<br><br>48 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG, BMI, body weight, safety | Primary:<br>At trial end, insulin glargine resulted in a significantly greater reduction in $HbA_{1c}$ compared to pioglitazone (-2.48 vs -1.86%; 95% CI, -0.93 to -0.31; *P*=0.001).<br><br>Secondary:<br>Insulin glargine resulted in significantly greater reductions in FPG at all time points (trial end difference, -34.9 mg/dL; 95% CI, -47.6 to -22.2; *P*<0.0001).<br><br>Changes in weight and BMI were similar between the two treatments.<br><br>Compared to pioglitazone, insulin glargine resulted in a lower overall incidence of possibly treatment-emergent adverse events (12.0 vs 20.7%) and fewer study discontinuations (2.2 vs 9.1%), but a higher rate (per patient-year) of confirmed clinically relevant hypoglycemic episodes (4.97 vs 1.04; *P*<0.0001) and severe hypoglycemia (0.07 vs 0.01; *P*=0.0309). |
| Perez-Monteverde et al.[73] (2011)<br><br>Sitagliptin/ metformin<br><br>vs<br><br>pioglitazone 30 to 45 mg QD<br><br>In Phase 1, patients were randomized to either sitagliptin 100 mg QD or pioglitazone 30 mg QD. In Phase 2, | DB, RCT<br><br>Patients with type 2 diabetes and $HbA_{1c}$ 7.5 to 12.0% | N=492 (Phase 1)<br><br>12 weeks (Phase 1) plus 28 weeks (Phase 2) | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and two-hour PPG, proportion of patients achieving $HbA_{1c}$ <7.0%, safety, body weight | Primary:<br>At the end of Phase 1 (12 weeks), mean changes from baseline in $HbA_{1c}$ were -1.0 and -0.9% with sitagliptin and pioglitazone. At the end of Phase 2 (40 weeks), improvements in $HbA_{1c}$ were greater with combination therapy compared to pioglitazone (-1.7 vs -1.4%; P=0.002).<br><br>Secondary:<br>At the end of Phase 1 (12 weeks), mean changes from baseline were -26.6 and -28.0 mg/dL for FPG and -52.8 and -50.1 mg/dL for two-hour PPG. At the end of Phase 2 (40 weeks), improvements in FPG and two-hour PPG were greater with combination therapy compared to pioglitazone (-45.8 vs -37.6 mg/dL; P=0.03 and -90.3 vs -69.1 mg/dL; P=0.001).<br><br>Significantly more patients receiving combination therapy achieved an $HbA_{1c}$ <7.0% (55.0 vs 40.5%; P=0.004).<br><br>A numerically higher incidence of gastrointestinal adverse events and a significantly lower incidence of oedema were observed with combination therapy compared to pioglitazone. The incidence of hypoglycemia was |

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| patients randomized to sitagliptin in Phase 1 were switched to sitagliptin/ metformin, and patients randomized to pioglitazone in Phase 1 were up titrated to 45 mg/day | | | | similarly low with both treatments.<br><br>Body weight decreased with combination therapy and increased with pioglitazone (-1.1 vs 3.4 kg; P<0.001). |
| Wainstein et al.[74] (2012)<br><br>Sitagliptin/ metformin 50/500 mg BID, titrated up to 50/1,000 mg BID<br><br>vs<br><br>pioglitazone 30 mg/day, titrated up to 45 mg/day | DB, RCT<br><br>Treatment-naïve patients with type 2 diabetes $HbA_{1c}$ 7.5 to 12.0% | N=517<br><br>32 weeks | Primary:<br>Change from baseline $HbA_{1c}$, proportion of patients who achieved $HbA_{1c}$ <7.0%<br><br>Secondary:<br>Change from baseline FPG | Primary:<br>The least squares mean changes in $HbA_{1c}$ at week 32 were -1.9 and -1.4% with combination therapy compared to pioglitazone, respectively (between-group differences, -0.5%; P<0.001).<br><br>A greater proportion of patients achieved an $HbA_{1c}$ <7.0% at week 32 with combination therapy compared to pioglitazone (57 vs 43%; P<0.001).<br><br>Secondary:<br>Compared to pioglitazone, combination therapy resulted in a greater least squares mean reductions in FPG (-56.0 vs -44.0 mg/dL; P<0.001) and 2-hour PPG (-102.2 vs -82.0 mg/dL; P<0.001) at week 32. A substantially greater reduction in FPG (-40.5 vs -13.0 mg/dL; P<0.001) was observed at week 1 with combination therapy compared to pioglitazone.<br><br>A greater reduction in the fasting proinsulin:insulin and a greater increased in HOMA-B were observed with combination therapy compared to pioglitazone, while greater decreases in fasting insulin and HOMA-IR, and a greater increase in quantitative insulin sensitivity check index were observed with pioglitazone compared to combination therapy.<br><br>Combination therapy resulted in a decrease in body weight (-1.4 kg) and pioglitazone resulted in an increase in body weight (3.0 kg; P<0.001).<br><br>Higher incidences of diarrhea (15.3 vs 4.3%; P<0.001), nausea (4.6 vs |

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| | | | | 1.2%; P=0.02), and vomiting (1.9 vs 0.0%; P=0.026), and a lower incidence of oedema (1.1 vs 7.0%; P<0.001) were observed with combination therapy compared to pioglitazone.<br><br>There was no difference between the two treatments in the incidence of hypoglycemia (8.4 vs 8.3%; P=0.055). |
| Borges et al.[75] (2011)<br><br>Rosiglitazone/ metformin<br><br>vs<br><br>metformin | DB, MC, RCT<br><br>Drug naïve patients with type 2 diabetes | N=688<br><br>18 months | Primary:<br>Change in baseline $HbA_{1c}$, FPG<br><br>Secondary:<br>Bone mineral density | Primary:<br>Combination therapy was more efficacious in achieving significant reductions in $HbA_{1c}$ (P<0.0001) and FPG (P<0.001) compared to metformin. In addition, more patients achieved $HbA_1c$ and FPG goals with combination therapy compared to metformin.<br><br>Secondary:<br>In a bone substudy, at week 80 combination therapy was associated with significantly lower BMD compared to metformin in the lumbar spine (P<0.0012) and total hip (P=0.0005, respectively). There was no difference between treatments for distal one-third of radius, femoral neck, and total bone mineral densities (P values not reported). |
| Fonseca et al.[76] (2000)<br><br>Rosiglitazone 4 mg and metformin 2,500 mg daily<br><br>vs<br><br>rosiglitazone 8 mg and metformin 2,500 mg daily<br><br>vs<br><br>metformin 2,500 mg daily | DB, PC, RCT<br><br>Patients with poorly controlled type 2 diabetes (mean FPG 140 to 300 mg/dL) with metformin; baseline $HbA_{1c}$ 8.6% in the metformin treatment group, 8.9% in the rosiglitazone/ metformin 4/2,500 mg treatment group and 8.9% in the rosiglitazone/ metformin 8/2,500 mg treatment group; patients were | N=348<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$, FPG, fructosamine, C-peptide, FFA, lipids, lactate, and estimates of insulin sensitivity (HOMA-S) and β-cell function (HOMA-B)<br><br>Secondary:<br>Not reported | Primary:<br>Addition of rosiglitazone significantly reduced $HbA_{1c}$ in a dose-related fashion from baseline compared to metformin monotherapy. Mean difference from the metformin control group was -1.0% (P<0.001) with rosiglitazone/metformin 4/2,500 mg and -1.2% with rosiglitazone/metformin 8/2,500 mg (P<0.001).<br><br>Mean FPG concentrations were reduced significantly with rosiglitazone/metformin 4/2,500 mg (-33 mg/dL; P<0.0001) and with rosiglitazone/metformin 8/2,500 mg (-48.4 mg/dL; P<0.0001). No significant change in FPG was observed with metformin monotherapy.<br><br>Fructosamine levels were reduced with both rosiglitazone/metformin 4/2,500 mg (-27.9 µmol/L; P value not reported) and rosiglitazone/metformin 8/2,500 mg (-36.8 µmol/L; P value not reported). Fructosamine levels increased with metformin monotherapy (12.3 µmol/L; P value not reported).<br><br>C-peptide values were reduced significantly in all treatment groups |

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| | excluded if they had NYHA class III-IV heart failure, angina, renal or liver disease, symptomatic neuropathy, or prior use of rosiglitazone or insulin | | | compared to baseline (P<0.05).<br><br>FFA levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).<br><br>Significant increases in TC, HDL-C and LDL-C were observed with both rosiglitazone groups when compared to metformin monotherapy group (P<0.05).<br><br>Mean fasting lactate levels were significantly less in both rosiglitazone/metformin groups compared to metformin monotherapy group (P<0.05).<br><br>Both insulin sensitivity (as measured by HOMA-S) and β-cell function (as measured by HOMA-B) were increased in a dose-dependent fashion with rosiglitazone/metformin compared to metformin monotherapy (P value not reported).<br><br>Secondary:<br>Not reported |
| Weissman et al.[77] (2005)<br><br>Rosiglitazone 8 mg QD and metformin 1,000 mg/day (RSG + MET)<br><br>vs<br><br>metformin 1,500 mg/day (MET) | DB, MC, PG, RCT<br><br>Patients 18 to 75 years of age diagnosed with type 2 diabetes (defined as $HbA_{1c}$ 6.5 to 8.5% for patients receiving combination therapy with metformin and sulfonylurea or $HbA_{1c}$ 7.0 to 10.0% for drug-naïve or patients receiving monotherapy), FPG of 126 to 270 | N=766<br><br>2-week wash out period followed by 4 to 7 weeks of run-in period and 24 weeks of treatment | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG at week 24, proportion of patients responding to treatment (reduction ≥0.7% for $HbA_{1c}$ and ≥30 mg/dL for FPG at week 24), clinical safety, adverse events, tolerability, clinical laboratory | Primary:<br>After 24 weeks, RSG+MET and MET were both effective in improving $HbA_{1c}$ with mean reductions of -0.93% (95% CI, -1.06 to -0.80) and -0.71% (95% CI, -0.83 to -0.60), respectively, with a mean treatment difference of -0.20% (95% CI, -0.36 to -0.04).<br><br>Secondary:<br>Significant reductions in FPG from baseline were seen in patients receiving RSG+MET (-2.29 mmol/L; 95% CI, -2.59 to -1.99) compared to patients receiving MET (-1.12 mmol/L; 95% CI, -1.43 to -0.82), with a treatment difference of -0.85 mmol/L (95% CI, -1.23 to -0.47).<br><br>The proportion of patients who responded to treatment (reduction in $HbA_{1c}$ ≥0.7%) was greater in the RSG+MET group than the MET group (59.5 and 49.5%, respectively) with the treatment difference of 10% (95% CI, 1.9 to 18.1). |

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| | mg/dL and BMI ≥27kg/m$^2$; any subjects previously receiving metformin or metformin and sulfonylurea must have received ≤metformin 1,000 mg/day for at least 3 months prior to study entry and patients must have stopped previous treatment with TZD at least 3 months prior to screening | | tests | The proportion of FPG responders (reduction in FPG ≥30 mg/dL) was also greater in the RSG+MET group than in the MET group (55.0 vs 32.5%, respectively).<br><br>The percentage of patients experiencing a gastrointestinal effect was greater in the MET group compared to the RSG+MET group (38.7 and 27.9%). The odds of experiencing a gastrointestinal side effect were 63% greater for patients receiving MET compared to patients receiving RSG+MET (OR, 1.63; 95% CI, 1.19 to 2.24).<br><br>RSG+MET resulted in a mean weight gain of 1.79 kg (P<0.0001) compared to a mean weight loss of -1.78 kg (P<0.001) with MET.<br><br>There were three deaths during the course of the study with two prior to DB study medication, and one while on RSG+MET; the cause of which was unknown, although it was not considered to be treatment related. |
| TODAY Study Group.[78] (2012) TODAY<br><br>Metformin<br><br>vs<br><br>rosiglitazone 4 mg BID plus metformin<br><br>vs<br><br>metformin plus lifestyle intervention (focusing on weight loss through eating and | MC, RCT<br><br>Patients 10 to 17 years of age, with type 2 diabetes | N=699<br><br>3.86 years (average follow-up) | Primary:<br>Loss of glycemic control ($HbA_{1c}$ ≥8.0% for six months or sustained metabolic decompensation requiring insulin)<br><br>Secondary:<br>Body weight, metabolic outcomes, safety | Primary:<br>Overall, a total of 319 (45.6%) patients reached the primary outcome, with a median time to treatment failure of 11.5 months (range, <1 to 66). Rates of failure were 51.7 (95% CI, 45.3 to 58.2), 38.6 (95% CI, 32.4 to 44.9), and 46.6% (95% CI, 40.2 to 53.0) of patients on metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention, respectively.<br><br>Rosiglitazone plus metformin was more efficacious to metformin; combination therapy was associated with a 25.3% decrease in the occurrence of the primary outcome compared to metformin (P=0.006). The outcome with metformin plus lifestyle intervention was intermediate, but not significantly different from metformin or rosiglitazone plus metformin (P value not reported). The reasons for treatment failure did not differ significantly across treatments.<br><br>Prespecified analyses according to sex and race or ethnic group showed differences in sustained effectiveness, with metformin least effective in non-Hispanic black patients and rosiglitazone plus metformin most effective in female patients.<br><br>Secondary: |

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| activity behaviors)<br><br>Patients were treated during a run-in period of 2 to 6 months with metformin 1,000 mg BID to attain an $HbA_{1c}$ <8.0% prior to randomization. | | | | BMI over time (up to 60 months) differed significantly according to the study treatment (P<0.001 for the overall comparison), and the results of all three pairwise comparisons between treatment groups were also significant. Patients treated with rosiglitazone plus metformin had the greatest increase in BMI and patients receiving metformin plus lifestyle intervention had the least.<br><br>The change in fat mass from baseline differed significantly across the treatment groups (P<0.05) because of a significant difference between rosiglitazone plus metformin and metformin plus lifestyle interventions. There were no significant between-group differences in the change from baseline for any other outcome.<br><br>Serious adverse events were reported in 19.2% of all patients, including 18.1, 14.6, and 24.8% with metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention (P=0.02). Hospitalizations accounted for more than 90% of serious adverse events. Severe hypoglycemia occurred in one, one, and two patients receiving metformin, rosiglitazone plus metformin, and metformin plus lifestyle intervention. No effects of rosiglitazone on bone mineral content or rate of fracture were noted. |
| Stewart et al.[79] (2006)<br><br>Rosiglitazone 8 mg QD and metformin 2,000 mg/day (MET + RSG)<br><br>vs<br><br>metformin 3,000 mg/day (MET) | DB, MC, PG, RCT<br><br>Type 2 diabetic patients 18 to 70 years of age, who were either antidiabetic-drug-naïve with FPG of 7.0 to 9.0 mmol/L and $HbA_{1c}$ 7.0 to 9.0%, or previously treated with oral antidiabetic monotherapy with FPG 6.0 to 8.0 mmol/L and $HbA_{1c}$ 6.5 to 8.0% | N=526<br><br>32 weeks | Primary:<br>Proportion of patients achieving $HbA_{1c}$ ≤6.5% at week 32, change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving target $HbA_{1c}$ and FPG levels, change in baseline FPG and fasting plasma insulin, change in insulin resistance, pancreatic β-cell | Primary:<br>At week 32, there was a reduction from baseline in mean $HbA_{1c}$ in the MET+RSG group from 7.2 to 6.7% compared to 7.2 to 6.8% in the MET group (P=0.0357).<br><br>Secondary:<br>The proportion of patients achieving $HbA_{1c}$ ≤6.5% at week 32 was similar in the two groups (P=0.095).<br><br>The proportion of patients achieving FPG <7.0 mmol/L at week 32 was 56% in the MET+RSG group compared to 38% in the MET group (OR, 2.33; P<0.0001).<br><br>The reduction in fasting plasma insulin from baseline was greater in the MET+RSG group compared to the MET group (treatment difference, -12.2 pmol/L; P=0.00029). |

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| | | | function, CRP, lipid parameters and 24-hour ambulatory BP, safety | HOMA-S, β-cell function, CRP, and SBP were greater in the MET+RSG group at week 32 compared to the MET group (P<0.05 for all).<br><br>TC, HDL-C, and LDL-C increased, FFAs decreased, and TG did not change in the MET+RSG group, whereas in the MET group there were decreases in TC, LDL-C, and TG, and increases in HDL-C and FFAs. The difference between the treatments was significant for the above parameters (P<0.05).<br><br>The proportion of patients with reductions in 24-hour mean SBP was greater in the MET+RSG group compared to the MET group (treatment difference, -3.6 mm Hg; P=0.0315).<br><br>The overall incidences of gastrointestinal adverse events were comparable between groups, but there was a lower incidence of diarrhea in the MET+RSG group (8 vs 18%). Hypoglycemia was reported in 17 patients (7%) in the MET+RSG group compared to 10 patients (4%) in the MET group.<br><br>There were greater reductions in mean hemoglobin and hematocrit over 32 weeks in the MET+RSG group compared to the MET group (P<0.0001). |
| Rosak et al.[80] (2005)<br><br>Rosiglitazone 4 to 8 mg and metformin (existing therapy) | OS, PM<br><br>Two studies in which type 2 diabetics on metformin therapy received rosiglitazone add-on therapy; baseline $HbA_{1c}$ was 8.1% in both trials | N=11,014<br><br>6 months | Primary:<br>Change in baseline $HbA_{1c}$, FPG, body weight, and BP<br><br>Secondary:<br>Not reported | Primary:<br>Addition of rosiglitazone significantly reduced $HbA_{1c}$ from baseline (-1.3%; P<0.0001).<br><br>Addition of rosiglitazone significantly reduced FPG from baseline (-47.0 mg/dL; P<0.0001).<br><br>Significant reduction in BP from baseline (-7/-3 mm Hg; P<0.0001) was observed with rosiglitazone add-on therapy.<br><br>Significant reduction in weight (-1.7 kg; P<0.0001) was observed with rosiglitazone add-on therapy.<br><br>Most commonly reported adverse events were weight gain (0.16%) and edema (0.15%). |

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| | | | | Secondary:<br>Not reported |
| Bailey et al.[81] (2005)<br><br>Rosiglitazone/ metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily<br><br>vs<br><br>metformin 2,500 to 3,000 mg daily | DB, MC, PG, RCT<br><br>Patients with type 2 diabetes poorly controlled (FPG ≥126 to 216 mg/dL) with metformin alone or in combination with an insulin secretagogue or acarbose; baseline $HbA_{1c}$ 7.4% for rosiglitazone add-on therapy and 7.5% for metformin; patients were excluded if they had been treated with a TZD or insulin, had unstable cardiovascular or cerebrovascular conditions, or had uncontrolled hypertension | N=568<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and insulin, proportion of patients who achieved $HbA_{1c}$ and FPG targets | Primary:<br>Reductions in $HbA_{1c}$ observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-0.22% difference between treatment groups; P=0.001).<br><br>Secondary:<br>Reductions in FPG observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (-18.3 mg/dL difference between treatment groups; P<0.001).<br><br>Significant reduction in fasting insulin was observed with rosiglitazone add-on therapy compared to metformin monotherapy (-12.4 pmol/L difference between treatment groups; P=0.001).<br><br>Greater proportion of patients on rosiglitazone add-on therapy (54%) reached $HbA_{1c}$ targets (<7.0%) compared to those treated with metformin monotherapy (36%; OR, 2.42; P<0.001).<br><br>Greater proportion of patients on rosiglitazone add-on therapy (32%) reached FPG targets (<126 mg/dL) compared to those treated with metformin monotherapy (8%; OR, 5.71; P<0.001).<br><br>Higher rate of withdrawal due to adverse events with metformin monotherapy (8 vs 4%; no P value reported) was noted. Gastrointestinal disorders were the most commonly reported event that caused withdrawal in the metformin monotherapy group. |
| Rosenstock et al.[82] (2006)<br><br>Rosiglitazone/ metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily | DB, MC, RCT<br><br>Type 2 diabetics with $HbA_{1c}$ >7.5 to 11.0%, with FPG ≤270 mg/dL who were previously treated with diet and exercise or had not | N=468<br><br>32 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ and FPG targets, change in | Primary:<br>Patients receiving rosiglitazone/metformin showed significant improvements in $HbA_{1c}$ with a reduction of -2.3% compared to baseline vs -1.8% with patients receiving metformin (P<0.0008) and -1.6% with patients receiving rosiglitazone (P<0.0001).<br><br>Secondary:<br>Target $HbA_{1c}$ ≤6.5 and <7.0% were achieved in more patients in the rosiglitazone/metformin group (60 and 77%) than in the metformin (39 |

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| vs<br><br>rosiglitazone 4 to 8 mg daily<br><br>vs<br><br>metformin 500 to 2,000 mg daily | been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening | | baseline FPG, safety | and 57%) or rosiglitazone (35 and 58%) groups, respectively (P values not reported).<br><br>The greatest mean decrease in FPG was seen with rosiglitazone/metformin (-74 mg/dL) and was significant compared to metformin (-50 mg/dL; P<0.0001) and rosiglitazone (-47 mg/dL; P<0.0001).<br><br>Treatment was well tolerated with nausea, vomiting and diarrhea as the most commonly reported adverse events. Edema was comparable between rosiglitazone/metformin (6%) and rosiglitazone (7%) and lower with metformin. |
| Hamann et al.[83] (2008)<br><br>Rosiglitazone/ metformin FDC 4 mg/2,000 mg daily (RSG+MET)<br><br>vs<br><br>glibenclamide‡ 5 mg and metformin 2,000 mg or gliclazide* 80 mg and metformin 2,000 mg daily (SU+MET) | DB, PG, RCT<br><br>Overweight patients (BMI ≥25 kg/m$^2$) with type 2 diabetes, $HbA_{1c}$ 7.0 to 10.0%, who received metformin ≥850 mg/day for at least 8 weeks | N=596<br><br>52 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to week 52<br><br>Secondary:<br>Change in FPG, β-cell function, insulin resistance, hypoglycemia, BP | Primary:<br>At week 52, mean change in $HbA_{1c}$ from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25).<br><br>Secondary:<br>Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095).<br><br>The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs 0.055 $HbA_{1c}$%/year, respectively; P=0.0002).<br><br>Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001).<br><br>Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001).<br><br>After 52 weeks, 24-hour diastolic and systolic ambulatory BP were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ambulatory BP (-2.9 mm Hg; P=0.0013), but not for systolic ambulatory BP (-2.6 mm Hg; P=0.0549). |
| Marre et al.[84] (2009)<br>LEAD-1 | AC, DB, DD, MC, PG, RCT<br><br>Type 2 diabetic | N=1,041<br><br>26 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>After 26 weeks, $HbA_{1c}$ decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: |

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| Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo<br><br>vs<br><br>placebo plus glimepiride 2 to 4 mg/day<br><br>vs<br><br>placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day | patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, $HbA_{1c}$ 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m$^2$ | | Secondary: Proportion of patients reaching $HbA_{1c}$ (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP | liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were more efficacious compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in $HbA_{1c}$ were greater in patients previously on an oral glucose lowering agent monotherapy.<br><br>Secondary:<br>The proportion of patients reaching $HbA_{1c}$ targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached $HbA_{1c}$ <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching $HbA_{1c}$ targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (P=0.018).<br><br>The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively).<br><br>The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported).<br><br>Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported). |

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| | | | | Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR.<br><br>Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported). |
| Rosenstock et al.[85] (2006)<br><br>Rosiglitazone/ metformin fixed dose combination 4/1,000 mg to 8/2,000 mg daily | MC, OL<br><br>Type 2 diabetics with $HbA_{1c}$ >11.0% or FPG >270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening | N=190<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients achieving $HbA_{1c}$ targets; change in baseline FPG, lipids, and insulin sensitivity (HOMA-S) | Primary:<br>Clinically significant mean reductions in $HbA_{1c}$ (11.8 to 7.8%; P<0.0001) were observed after initiation of rosiglitazone/metformin at week 24.<br><br>Secondary:<br>Treatment goals of $HbA_{1c}$ ≤6.5% and <7.0% at week 24 were achieved in 33 and 44% of patients, respectively.<br><br>Clinically significant mean reductions in FPG (304 to 166 mg/dL; P<0.0001) were observed after initiation of rosiglitazone/metformin at week 24.<br><br>HDL-C increased 4.4% and TC (-3.7%), LDL-C (-0.7%) and TG (-13.4%) decreased compared to baseline (P values not reported).<br><br>Rosiglitazone/metformin significantly increased HOMA estimates of insulin sensitivity by 68% (P<0.0001).<br><br>Rosiglitazone/metformin was well tolerated. There was a 2% incidence of hypoglycemia, mean increase in weight of 2.6 kg from baseline and 2.6% of patients withdrew because of an adverse event. |
| Fonseca et al.[86] (2003)<br><br>Rosiglitazone 8 mg QD and | DB, MC, PC, RCT<br><br>Patients ≥21 years of age with type 2 diabetes for ≥6 | N=402<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary: | Primary:<br>$HbA_{1c}$ did not change significantly from baseline in the placebo group, but did change significantly in the nateglinide group. The change from baseline to end point was -0.8±0.1% (P<0.0001 vs baseline or placebo). |

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| nateglinide 120 mg before each meal<br><br>vs<br><br>rosiglitazone 8 mg QD and placebo | months previously and treated with rosiglitazone 8 mg/day, diet, and exercise for ≥3 months, had a BMI 22 to 40 kg/m$^2$, FPG 6.1 to 13.3 mmol/L, and $HbA_{1c}$ 7.0 to 11.0% | | FPG, two-hour postprandial insulin, TC, LDL-C, HDL-C, TG, body weight, four-hour AUC for glucose, insulin during meal challenges | Secondary:<br>Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide group (P<0.001). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo.<br><br>Two-hour postprandial insulin in the nateglinide group decreased from 14.0 to 11.4 mmol/L (P<0.0001). The group receiving placebo had an increase in 2-hour postprandial insulin from 14.4 to 14.8 mmol/L (P<0.0001 vs nateglinide).<br><br>Total and incremental glucose $AUCs_{(0\text{-}4\ hours)}$ were significantly reduced in the nateglinide group (-8.6±0.8 and -6.2±0.5 mmol/L/hr, respectively; P<0.0001 vs baseline or placebo for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC.<br><br>Total and incremental insulin $AUCs_{(0\text{-}4\ hour)}$ were increased in the nateglinide group (425 and 395 pmol/L/hr, respectively; P<0.0001 vs baseline or placebo plus for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC.<br><br>There were no significant changes in TC, LDL-C, or TG in either group. There was a small, but significant increase from baseline in HDL-C observed in patients receiving nateglinide (P<0.025) and in patients receiving placebo (P<0.005).<br><br>Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide (3.1±0.3 kg) was significantly greater compared to patients receiving placebo (1.1±0.3 kg; P<0.0001).<br><br>Meal challenges were performed at week 0 and at end point. The glucose and insulin profiles were similar in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients receiving placebo. |
| Raskin et al.[87] (2004) | MC, OL, PG, RCT | N=252 | Primary:<br>Change in baseline | Primary:<br>Mean change in $HbA_{1c}$ from baseline with repaglinide was -0.17% and |

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| Rosiglitazone 2 to 4 mg BID and repaglinide 0.5 to 4 mg TID before meals<br><br>vs<br><br>rosiglitazone 2 to 4 mg BID<br><br>vs<br><br>repaglinide 0.5 to 4 mg TID before meals | Patients ≥18 years old with type 2 diabetes for ≥12 months with an $HbA_{1c}$ >7.0 to ≤12.0% during previous monotherapy with sulfonylurea or metformin for ≥3 months with a BMI ≤45 kg/$m^2$ | 24 weeks | $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG | -0.56% with rosiglitazone. The mean change in $HbA_{1c}$ from baseline with combination therapy was -1.43 (P≤0.001 vs either monotherapy). The reduction in $HbA_{1c}$ from baseline was greater with combination therapy compared to the sum of the responses for monotherapy (P<0.01).<br><br>Secondary:<br>Mean FPG change from baseline with repaglinide was -3 mmol/L and -3.7 mmol/L with rosiglitazone. Mean FPG change from baseline with combination therapy was -5.2 mmol/L (P≤0.001 vs either monotherapy). |
| McCluskey et al.[88] (2004)<br><br>Rosiglitazone (existing therapy) and glimepiride 2 to 8 mg QD<br><br>vs<br><br>rosiglitazone (existing therapy) | MC, PC, RCT<br><br>Patients with type 2 diabetes poorly controlled ($HbA_{1c}$ 7.5 to 9.5%) with rosiglitazone monotherapy | N=40<br><br>30 weeks | Primary:<br>Effect on $HbA_{1c}$<br><br>Secondary:<br>Effect on FPG, body weight, lipoproteins, proportion of patients who achieved $HbA_{1c}$ and FPG targets | Primary:<br>Significant reductions in $HbA_{1c}$ were observed with glimepiride (-1.2%) compared to placebo (-0.3%; P<0.001).<br><br>Secondary:<br>Significant reductions in FPG were observed with glimepiride (-24.41 mg/dL) compared to placebo (5.9 mg/dL; P<0.008).<br><br>Significantly greater proportion of patients receiving glimepiride achieved the target $HbA_{1c}$ ≤7.0% (60.0 vs 14.3%; P<0.008).<br><br>There were no significant differences between treatment groups in TC, HDL-C, LDL-C, or TG at any time during study period. |
| Rosenstock et al.[89] (2008)<br><br><u>Study A</u><br>Rosiglitazone 4 mg QD and glimepiride 3 mg | 2 DB, PC, RCT<br><br>Patients 40 to 80 years of age (Study A) or 18 to 75 years of age (Study B) with type 2 | N=174 (Study A)<br><br>N=391 (Study B)<br><br>26 weeks | Primary:<br>Mean change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients with | <u>Study A</u><br>Primary:<br>At week 26, the mean change in $HbA_{1c}$ from baseline was -0.63% in the RSG 4 mg+GLIM (P=0.03 vs GLIM 3 mg), -1.17% in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -0.08% in the GLIM 3 mg group. |

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| QD (RSG 4 mg + GLIM)<br><br>vs<br><br>rosiglitazone 8 mg QD and glimepiride 3 mg QD (RSG 8 mg + GLIM)<br><br>vs<br><br>glimepiride 3 mg QD (GLIM alone)<br><br><u>Study B</u><br>Rosiglitazone 4 mg QD and glimepiride 2 to 4 mg QD (RSG add-on)<br><br>vs<br><br>glimepiride 4 to 8 mg QD and placebo (GLIM) | diabetes, $HbA_{1c}$ ≥7.0% and FPG 126 to 270 mg/dL at baseline; in the 3 months prior to enrolment, eligible patients in Study A received monotherapy with an oral antidiabetic agent; eligible patients in Study B were treated with a non-TZD oral antidiabetic therapy for ≥3 months prior to screening, including metformin monotherapy, sulfonylurea monotherapy, or low-dose combination therapy with metformin and sulfonylurea | (Study A)<br><br>24 weeks<br>(Study B) | $HbA_{1c}$ <7.0% and/or $HbA_{1c}$ reduction ≥0.7% at the end of the treatment period, mean change in baseline FPG | Secondary:<br>The mean change in FPG from baseline was -21 mg/dL in the RSG 4 mg+GLIM (P=0.09 vs GLIM alone), -43 mg/dL in the RSG 8 mg+GLIM groups (P<0.0001 vs GLIM 3 mg), and -2 mg/dL for GLIM 3 mg.<br><br>At week 26, 43% of patients achieved $HbA_{1c}$ <7.0% in the RSG 4 mg+GLIM group (P=0.0129 vs GLIM alone) and 68% achieved the same $HbA_{1c}$ goal in the RSG 8 mg+GLIM group (P=0.0001 vs GLIM 3 mg) compared to 32% in the GLIM 3 mg.<br><br><u>Study B</u><br>Primary:<br>At week 24, the mean change in $HbA_{1c}$ from baseline was -0.68% in the RSG add-on group compared to -0.08% in the GLIM 4 to 8 mg group (P<0.0001).<br><br>Secondary:<br>The mean change in FPG from baseline was -28 mg/dL in the RSG add-on group compared to -1 mg/dL in the GLIM 4 to 8 mg group (P<0.0001).<br><br>At week 24, 39% of patients achieved $HbA_{1c}$ <7.0% in the RSG add-on group compared to 15% in the GLIM 4 to 8 mg group (P<0.0001).<br><br>Insulin sensitivity increased significantly in the RSG add-on group but was unchanged with GLIM 4 to 8 mg. β-cell function increased over 24 weeks in both treatment groups but with a significantly greater increase with RSG add-on group.<br><br>RSG add-on significantly reduced fasting levels of C-peptide (P=0.025), proinsulin (P=0.0006), and insulin (P=0.013) and reduced the proinsulin: insulin ratio (P<0.0001). There were no significant changes in any of these parameters with GLIM 4 to 8 mg (C-peptide; P=0.075, proinsulin; P=0.42, insulin; P=0.10 and proinsulin:insulin ratio; P=0.34). |
| Chou et al.[90] (2008)<br><br>Rosiglitazone/ | DB, MC, PG, RCT<br><br>Type 2 diabetics, $HbA_{1c}$ 7.5 to 12.0%, | N=901<br><br>28 weeks | Primary:<br>Change in baseline $HbA_{1c}$ | Primary:<br>Both rosiglitazone/glimepiride regimens significantly reduced $HbA_{1c}$ to a greater extent than glimepiride or rosiglitazone monotherapy regimens (P<0.0001). |

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| glimepiride fixed dose combination 4/1 mg titrated to 4/4 mg (regimen A) or titrated to 8/4 mg QD (regimen B) (RSG/GLIM)<br><br>vs<br><br>rosiglitazone 4 mg titrated to 8 mg QD (RSG)<br><br>vs<br><br>glimepiride 1mg titrated to 4 mg QD (GLIM) | fasting C-peptide ≥0.8 ng/mL, FPG ≥126 mg/dL, who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months | | Secondary:<br>Change in baseline FPG, proportion of patients achieving $HbA_{1c}$ and FPG targets, HOMA-S, HOMA-B, cardiovascular biomarkers, safety | Secondary:<br>A significantly greater reduction in FPG levels was observed in the rosiglitazone/glimepiride group compared to the glimepiride or rosiglitazone monotherapy groups (P<0.0001).<br><br>Significantly more patients achieved $HbA_{1c}$ target levels ≤6.5 and <7.0% with either rosiglitazone/glimepiride regimen than patients with glimepiride or rosiglitazone monotherapy regimens (P<0.0001).<br><br>Improvement in CRP was also observed in patients treated with rosiglitazone/glimepiride or rosiglitazone monotherapy compared to patients treated with glimepiride monotherapy (P<0.05).<br><br>There were no new safety or tolerability issues identified from its monotherapy components and a similar adverse event profile was observed across the fixed-dose regimens. The most commonly reported adverse event was hypoglycemia and the incidence of confirmed symptomatic hypoglycemia (3.6 to 5.5%) was comparable among subjects treated with a fixed-dose regimen and glimepiride monotherapy. |
| Home et al.[91] (2007)<br><br>Rosiglitazone plus either metformin or a sulfonylurea<br><br>vs<br><br>metformin plus a sulfonylurea | MC, OL, PG, RCT<br><br>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | N=1,122<br><br>18 months | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>FPG, serum lipids, HOMA basal insulin sensitivity and islet β-cell function (HOMA %β), body weight, inflammatory/ thrombotic markers, CRP | Primary:<br>At 18 months, $HbA_{1c}$ reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference, 0.07%; 95% CI, -0.09 to 0.23; P value not significant), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference, 0.06%; 95% CI, -0.09 to 0.20; P value not significant).<br><br>Secondary:<br>Differences in FPG were not significant at 18 months (rosiglitazone vs sulfonylurea, -0.36 mmol/L; P=0.062 and rosiglitazone vs metformin, -0.34 mmol/L; P=0.089).<br><br>Rosiglitazone increased TC (P≤0.001) and LDL-C (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared to the control. An increase in HDL-C and TG was observed with rosiglitazone compared to sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001, 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (P value not significant for |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | both).<br><br>HOMA-estimated basal insulin sensitivity was substantially increased with rosiglitazone compared to the respective controls (P<0.001 for both). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, to a similar extent (P value not significant).<br><br>Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003).<br><br>At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (-5.7 vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P value not significant).<br><br>There was a significant reduction in CRP with rosiglitazone compared to a sulfonylurea (P<0.001) and metformin (P=0.001). |
| Komajda et al.[92] (2008)<br><br>Rosiglitazone plus either metformin or a sulfonylurea<br><br>vs<br><br>metformin plus a sulfonylurea | MC, OL, RCT (RECORD)<br><br>Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m$^2$, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control ($HbA_{1c}$ 7.0 to 9.0%) | N=668<br><br>12 months | Primary:<br>Change from baseline in 24-hour ambulatory BP at six months and 12 months<br><br>Secondary:<br>Not reported | Primary:<br>For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour SBP was greater at six months (-3.8 mm Hg) and 12 months (-3.8 mm Hg) than with metformin and sulfonylurea therapy (-1.2 mm Hg and -1.3 mm Hg, respectively; six months, P=0.015; 12 months, P=0.031).<br><br>Reductions in 24-hour DBP were greater at six months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mm Hg) compared to metformin and sulfonylurea (-0.4 mm Hg and -0.6 mm Hg; both P<0.001).<br><br>At 12 months, the reduction in 24-hour SBP was greater for rosiglitazone and metformin (-4.9 mm Hg) than for metformin and sulfonylurea (-2.2 mm Hg; P=0.016).<br><br>At 12 months, the reduction in DBP was greater for rosiglitazone and metformin (-3.8 mm Hg) than for metformin and sulfonylurea (-1.7 mm Hg; P=0.003). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | At six months, the reductions in SBP and DBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (SBP; P=NS, DBP; P=0.049).<br><br>Secondary:<br>Not reported |
| Scott et al.[93] (2008)<br><br>Rosiglitazone 8 mg once daily and metformin (existing therapy)<br><br>vs<br><br>sitagliptin 100 mg once daily and metformin (existing therapy)<br><br>vs<br><br>metformin (existing therapy) and placebo | AC, DB, MC, PG, RCT<br><br>Type 2 diabetics 18 to 75 years of age receiving stable metformin doses (≥1,500 mg/day for ≥10 weeks) and inadequate glycemic control ($HbA_{1c}$ ≥7.0 and ≤11.0%) | N=273<br><br>18 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary: Change in baseline FPG, fasting serum insulin, fasting serum proinsulin, β cell function, insulin resistance, and lipid profile | Primary:<br>Sitagliptin significantly decreased $HbA_{1c}$ compared to placebo (treatment difference, -0.50%; 95% CI, -0.87 to -0.60; P≤0.001). Similar results were observed with rosiglitazone (treatment difference, -0.57%; 95% CI, -0.76 to -0.37; P value not reported). There was no difference between sitagliptin and rosiglitazone (treatment difference, -0.06%; 95% CI, -0.25 to 0.14).<br><br>The proportion of patients achieving an $HbA_{1c}$<7.0% was significantly greater with sitagliptin (55%; P=0.006) and rosiglitazone (63%; P value not reported) compared to placebo (38%). There was no difference between sitagliptin and rosiglitazone (treatment difference, 8%; 95% CI, -6 to 22; P value not reported).<br><br>Secondary:<br>Sitagliptin (treatment difference, -17.8 mg/dL; 95% CI, -27.6 to -8.1; P≤0.001) and rosiglitazone (treatment difference, -30.6 mg/dL; 95% CI, -40.6 to -20.7; P value not reported) significantly decreased FPG compared to placebo.<br><br>Rosiglitazone significantly decreased FPG compared to sitagliptin (treatment difference, -12.8 mg/dL; 95% CI, -22.6 to -3.0; P value not reported).<br><br>Sitagliptin (treatment difference, 16.3; 95% CI, 2.3 to 30.3; P≤0.05) and rosiglitazone (treatment difference, 15.3; 95% CI, 1.0 to 29.6; P value not reported, respectively) had significant increases in HOMA-B compared to placebo. The increase in HOMA-B was not significantly different between sitagliptin and rosiglitazone (P value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | Rosiglitazone significantly decreased HOMA-IR compared to placebo (treatment difference, -2.4; 95% CI, -3.4 to -1.4; P value not reported) and sitagliptin (treatment difference, -1.6; 95% CI, -2.6 to -0.7; P value not reported). There decrease in HOMA-IR was similar between sitagliptin and placebo (treatment difference, -0.7; 95% CI, -1.7 to 0.2; P value not reported).<br><br>Rosiglitazone significantly decreased fasting serum insulin compared to placebo (treatment difference, -3.4 µIU/mL; 95% CI, -5.5 to -1.4; P value not reported) and sitagliptin (treatment difference, -3.53 µIU/mL; 95% CI, -5.50 to -1.40; P value not reported).<br><br>The proinsulin:insulin ratio was similar across all treatments.<br><br>Compared to placebo, LDL-C decreased with sitagliptin (treatment difference, -5.3 mg/dL; 95% CI, -14.5 to 3.9; P value not reported) and increased with rosiglitazone (treatment difference, 9.5 mg/dL; 95% CI, 0.2 to 18.7; P value not reported). Compared to placebo, TC significantly decreased with sitagliptin (treatment difference, -6.3 mg/dL; 95% CI, -11.8 to -0.9; P≤0.05) and increased with rosiglitazone (treatment difference, 5.1 mg/dL; 95% CI, -0.3 to 10.6; P value not reported). Compared to placebo, TG significantly decreased with sitagliptin (treatment difference, -16.7 mg/dL; 95% CI, -27.9 to 5.5; P≤0.05) and increased with rosiglitazone (treatment difference, 1.2 mg/dL; 95% CI, -10.1 to 12.6; P value not reported). Compared to sitagliptin, lipid profiles measurements significantly increased with rosiglitazone (P values not reported). |
| Rigby et al.[94] (2010)<br><br>Rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy)<br><br>vs | OL<br><br>Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control ($HbA_{1c}$ 6.5 to 10.0% on a stable regimen of | N=169<br><br>16 weeks | Primary:<br>Change in $HbA_{1c}$ from baseline to week 16<br><br>Secondary:<br>Change in $HbA_{1c}$ from baseline to week eight, change in fasting plasma | Primary:<br>At week 16, $HbA_{1c}$ was reduced from baseline in all treatment groups (least square mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009).<br><br>Secondary:<br>At week eight, $HbA_{1c}$ was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| sitagliptin 100 mg QD and metformin (existing therapy)<br><br>vs<br><br>colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy) | metformin (1,500-2,550 mg daily), with LDL-C ≥60 mg/dL and TG <500 mg/dL | | glucose and fasting insulin from baseline to weeks eight and 16, change in two-hour PPG and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an $HbA_{1c}$ reduction >0.7% from baseline, percentage of participants who achieved $HbA_{1c}$ <7.0% | Fasting plasma glucose was significantly reduced from baseline at week eight and week 16 in all treatment groups.<br><br>The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups.<br><br>There was no significant change in fasting insulin or two-hour postprandial insulin from baseline to week 16 in any treatment group.<br><br>Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008).<br><br>LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011).<br><br>TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median TG levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect triglyceride levels. HDL-C levels did not change significantly from baseline with any treatment.<br><br>At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in $HbA_{1c}$ 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved $HbA_{1c}$ <7.0%.<br><br>The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | severity. |
| Hollander et al.[95] (2009)<br><br>Thiazolidinedione (existing therapy) and saxagliptin 2.5 mg QD<br><br>vs<br><br>thiazolidinedione (existing therapy) and saxagliptin 5 mg QD<br><br>vs<br><br>thiazolidinedione (existing therapy) and placebo | DB, MC, RCT<br><br>Type 2 diabetics 18 to 77 years of age with inadequate glycemic control ($HbA_{1c}$ ≥7.0 to ≤10.5%) receiving stable doses of TZD (pioglitazone 30 or 45 mg/day or rosiglitazone 4 or 8 mg/day for ≥12 weeks), fasting C-peptide ≥0.3 nmol/L, and BMI ≤45 kg/m$^2$ | N=565<br><br>24 weeks | Primary:<br>Change in baseline $HbA_{1c}$<br><br>Secondary:<br>Change in baseline FPG and PPG $AUC_{0\text{-}3hr}$, proportion of patients achieving an $HbA_{1c}$ <7.0% | Primary:<br>Saxagliptin significantly decreased $HbA_{1c}$ compared to placebo (saxagliptin 2.5 mg, -0.66%; treatment difference, -0.36%; P<0.0007 vs placebo and saxagliptin 5 mg, -0.94%; treatment difference, -0.63%; P<0.0001 vs placebo).<br><br>Secondary:<br>Saxagliptin significantly decreased FPG compared to placebo (saxagliptin 2.5 mg treatment difference, -0.8 mmol/L; P<0.0053 vs placebo and saxagliptin 5 mg treatment difference, -1.0 mmol/L; P=0.0005 vs placebo).<br><br>A significantly greater proportion of patients receiving saxagliptin achieved an $HbA_{1c}$ <7.0% compared to patients receiving placebo (42.2 [P=0.0010] and 41.8 [P=0.0013] vs 25.6%).<br><br>Saxagliptin significantly decreased PPG $AUC_{0\text{-}3hr}$ compared to placebo (P<0.0001 for both). Similar results were observed with PPG $AUC_{0\text{-}2hr}$ (P<0.0001 for both).<br><br>Overall, saxagliptin was well tolerated. The proportion of patients experiencing any adverse effect was 68.0 vs 66.8%, with the highest frequency with saxagliptin 5 mg. The frequency of hypoglycemic events was similar between the two treatments (3.4 vs 3.8%). The most commonly reported adverse events were upper respiratory tract infection, peripheral edema, and headache. |
| Pinelli et al.[96] (2008)<br><br>Thiazolidinediones in combination with other antidiabetic agents<br><br>vs | MA (22 RCTs)<br><br>Patients with type 2 diabetes receiving combination therapy | N=9,325<br><br>≥24 weeks | Primary:<br>Mean change in baseline $HbA_{1c}$<br><br>Secondary:<br>Proportion of patients reaching $HbA_{1c}$ <7.0%, mean change from | Primary:<br>There were small reductions in $HbA_{1c}$ across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide.<br><br>When only PC trials were analyzed, there were greater reductions in $HbA_{1c}$ with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83).<br><br>When only TZD AC trials were analyzed, there was a significant |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| exenatide in combination with other antidiabetic agents | | | baseline in FPG and body weight, hypoglycemia, gastrointestinal adverse events | difference in $HbA_{1c}$ levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01).<br><br>There was no difference in $HbA_{1c}$ reduction between exenatide and insulin comparators in OL, non-inferiority trials.<br><br>Secondary:<br>TZD and exenatide-based therapies were associated with OR of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching $HbA_{1c}$ <7.0%.<br><br>FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31).<br><br>Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32).<br><br>In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64).<br><br>The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and |

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| | | | | 4% in patients receiving comparator. |
| Clar et al.[97] (2009)<br><br>Pioglitazone vs<br><br>no additional treatment<br><br>All patients were receiving insulin (with or without other oral hypoglycemic agents). | MA<br><br>Patients with type 2 diabetes | N=3,092 (8 trials)<br><br>≥12 weeks | Primary:<br>$HbA_{1c}$, frequency of hypoglycemia, total daily dose of insulin, weight changes, changes in cardiovascular risk factors, and adverse events<br><br>Secondary:<br>Not reported | Primary:<br>$HbA_{1c}$ values were significantly lower in the groups taking pioglitazone plus insulin than in the groups taking insulin without pioglitazone (weighted mean difference -0.58%, 95% CI: -0.70 to -0.46; P<0.00001).<br><br>There were more patients with hypoglycemic episodes in the pioglitazone plus insulin groups than with insulin without pioglitazone; however, this difference was not statistically significant (relative risk 1.27, 95% CI: 0.99 to 1.63, P=0.06).<br><br>Insulin dose ranged between 42 to 64 U/day or 0.5 to 1 U/kg/day in the pioglitazone groups and between 55 to 70 U/day and 0.7 to 1.2 U/kg/day in the groups taking no pioglitazone.<br><br>Weight change ranged between +1.4 and +4.4 kg in the pioglitazone plus insulin groups and between -0.04 and +4.9 kg in the insulin only groups.<br><br>Four studies reported results for serum TGs. Only two of the studies demonstrated a significant reduction in the pioglitazone groups (-0.44 to -0.70 mmol/L) compared to insulin only). None of the studies found a difference in TC between the pioglitazone plus insulin and the insulin without pioglitazone groups. Four studies reported on HDL-C and all found significantly increased values in the pioglitazone groups (+0.10 mmol/L to +0.18 mmol/L) compared to insulin only. None of the studies found a difference in LDL-C between the pioglitazone plus insulin and the insulin without pioglitazone groups.<br><br>Besides weight gain and hypoglycemia, the only adverse event reported as occurring more frequently with pioglitazone was peripheral edema. |
| **Diabetes Prevention Trials** | | | | |
| Zinman et al.[98] (2010)<br>CANOE<br><br>Rosiglitazone 2 mg/day plus | DB, RCT<br><br>Patients with impaired glucose tolerance | N=207<br><br>3.9 years (median duration) | Primary:<br>Time to development of diabetes<br><br>Secondary: | Primary:<br>Incident diabetes occurred in significantly fewer patients receiving combination therapy compared to placebo (14 vs 39%; P<0.0001). The relative risk reduction was 66% (95% CI, 48 to 80) and the absolute risk reduction was 26% (95% CI, 14 to 37), yielding a number needed to treat of 4 (95% CI, 2.70 to 7.14). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| metformin 500 mg BID<br><br>vs<br><br>placebo | | | Insulin sensitivity, β cell function, safety | Seventy patients (80%) receiving combination therapy regressed to normal glucose tolerance compared to 52 patients (53%) receiving placebo (P=0.0002).<br><br>Secondary:<br>Insulin sensitivity decreased by trial end in patients receiving placebo (median, -1.24) and remained unchanged in patients receiving combination therapy (median, -0.39; P=0.0006 vs placebo).<br><br>Change in β cell function did not differ between the two treatments (P=0.28).<br><br>Significantly more patients receiving combination therapy experienced diarrhea compared to placebo (P=0.0253). |
| Gerstein et al.[99] (2006)<br>DREAM<br><br>Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily<br><br>vs<br><br>placebo | MC, PRO, RCT<br><br>Adults ≥30 years of age or more with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease; people with a history of diabetes (except gestational diabetes), cardiovascular disease or intolerance to either angiotensin-converting enzyme inhibitors or TZDs were excluded | N=5,269<br><br>Median 3 years (range, 2.5 to 4.7 years) | Primary:<br>Composite of incident diabetes or death<br><br>Secondary:<br>Regression to normoglycemia, composite of cardiovascular events (e.g., MI, stroke, cardiovascular death, revascularization procedures and heart failure) and glucose concentrations | Primary:<br>The composite primary outcome was observed in 11.6% of individuals given rosiglitazone and 26.0% of individuals given placebo (HR, 0.40; 95% CI, 0.35 to 0.46; P<0.0001). There was no difference in the number of deaths (HR, 0.91; 95% CI, 0.55 to 1.49; P=0.7). The frequency of diabetes was reported in significantly fewer patients receiving rosiglitazone than those receiving placebo (HR, 0.38; 95% CI, 0.33 to 0.44; P<0.0001).<br><br>Secondary:<br>Normoglycemia was reported in 1,330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) participants in the placebo group (HR, 1.71; 95% CI, 1.57 to 1.87; P<0001).<br><br>The frequency of composite cardiovascular outcome was similar between rosiglitazone and placebo. The components of the composite were similar between the two groups with the exception of heart failure, which was reported in 14 (0.5%) participants in the rosiglitazone group and two (0.1%) participants in the placebo group (P=0.01).<br><br>The median fasting plasma glucose concentration was 0.5 mmol/L lower in the rosiglitazone group than in the placebo group (P<0.0001); the two- |

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| | | | | hour plasma glucose concentration was 1.6 mmol/L lower with rosiglitazone than placebo (P<0.0001). |
| Dagenais et al.[100] (2008)<br>DREAM<br><br>Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily<br><br>vs<br><br>placebo | MC, PRO, RCT<br><br>Adults ≥30 years of age with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease | N=5,269<br><br>3 years | Primary:<br>Composite cardiovascular outcome, composite renal outcome<br><br>Secondary:<br>Not reported | Primary:<br>During the three year follow-up, 836 patients had a first occurrence of the composite cardiorenal outcome (2.5% cardiovascular composite outcomes and 13.6% renal composite outcomes).<br><br>The composite cardiorenal outcome occurred in 15.0% of patients receiving rosiglitazone and 16.8% of patients receiving placebo (HR, 0.87; 95% CI, 0.75 to 1.01; P=0.07).<br><br>Rosiglitazone did not reduce the overall risk of cardiovascular events, but significantly increased the risk for heart failure (0.5%) compared to placebo (0.1%; 95% CI, 1.60 to 31.0).<br><br>Rosiglitazone reduced the renal component of the composite outcome by 20% due to a reduction in progression of albuminuria compared to placebo (HR, 0.80; 95% CI, 0.68 to 0.93; P=0.031). The fall in estimated glomerular filtration rate by ≥30% was not significant (P=0.087).<br><br>Secondary:<br>Not reported |

*Not available in the United States.
†Estimates approximate values since results were displayed in bar graph and precise values were not reported.
‡Synonym for glyburide.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SC=subcutaneous, TID=three times daily
Study design abbreviations: AC=active-comparator, DB=double-blind, DD=double-dummy, MA=meta analysis, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, SR=systematic review, XO=cross-over
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo=apolipoprotein, AUC=area under the curve, BMD=bone mineral density, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, CI=confidence interval, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, $HbA_{1c}$=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA=homeostasis model assessment, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, HR=hazard ratio, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MACE=major adverse cardiovascular events, MI=myocardial infarction, NPH=neutral protamine Hagedorn, NYHA=New York Heart Association, OR=odds ratio, PGWB=psychological general well-being, PPAR=peroxisome proliferator-activated receptor, PPG=post-prandial glucose, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TZD=thiazolidinedione, VLDL=very low density lipoprotein cholesterol, WMD=weighted mean difference

**Additional Evidence**

Dose Simplification
Vanderpoel at al. investigated the adherence rates with the fixed-dose combination of rosiglitazone and metformin compared to monotherapy or concomitant administration of the individual components. Prescription claims for 16,929 type 2 diabetics were analyzed for a 12-month time period. Adherence pre- and post-index was measured by a medication possession ratio, a proxy measurement to determine adherence. Compared to the pre-index period for concomitant administration of the individual components, the fixed-dose combination product had a significant increase in the medication possession ratio (+4.8; P<0.005). There was no significant difference in pill burden, insulin use rate, or non-study oral hyperglycemic agents between the two groups.[101]

Stable Therapy
Berhanu et el. evaluated changes in lipid profiles in 305 patients with type 2 diabetes and dyslipidemia after treatment conversion from rosiglitazone to pioglitazone with continuation of statin and other lipid-lowering therapies. At 17 weeks after treatment conversion from rosiglitazone to pioglitazone, patients had significant reductions in triglycerides (–15.2%; P<0.0001), total cholesterol (–9.0%; P<0.0001), and low-density lipoprotein (LDL) particle concentration (–189 nmol/L; P<0.0001) without significant changes in $HbA_{1c}$ (0.02%). LDL cholesterol (+2.2%), high-density lipoprotein cholesterol (+1.8%; P<0.05), and LDL particle diameter (+0.23 nm; P<0.0001) increased as well.[102]

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 15. Relative Cost of the Thiazolidinediones**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| **Single Entity Agents** | | | | |
| Pioglitazone | tablet | Actos®* | $$$$$ | $$$-$$$$ |
| Rosiglitazone | tablet | Avandia® | $$$$$ | N/A |
| **Combination Products** | | | | |
| Pioglitazone and glimepiride | tablet | Duetact® | $$$$$ | N/A |
| Pioglitazone and metformin | tablet | Actoplus Met®*, Actoplus Met XR® | $$$$$ | $$$$$ |
| Rosiglitazone and | tablet | Avandaryl® | $$$$ | N/A |

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| glimepiride | | | | |
| Rosiglitazone and metformin | tablet | Avandamet® | $$$$$ | N/A |

N/A=Not available

## X. Conclusions

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-6] There are no generic products available; however, metformin and glimepiride are available generically in a separate formulation.

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high $HbA_{1c}$ will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The thiazolidinediones are noted to be associated with weight gain, fluid retention, congestive heart failure, and fractures. The thiazolidinediones are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. However, due to the mechanisms of action of the thiazolidinediones and metformin, the addition of an incretin mimetic, dipeptidyl peptidase-4 (DPP-4) inhibitor, or secretagogue is preferred over a thiazolidinedione to be added to metformin. In addition, the combination of metformin and a thiazolidinedione, while efficacious, carries risks of adverse events associated with both agents. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DDP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. In general, recommendations regarding the thiazolidinediones are made for the medication class as a whole; however, more recent guidelines from the American Diabetes Association/European Association for the Study of Diabetes do not recommend rosiglitazone.[9-18]

A variety of clinical trials have been conducted with the thiazolidinediones.[19-102] In comparative studies, the use of pioglitazone and rosiglitazone led to similar improvements in glycemic control.[38,39,41,43,44,56] Several studies evaluated the efficacy of thiazolidinediones in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[59-62,73-79,86-89,95] However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.[63-71,83,91,93] The thiazolidinedione fixed-dose combination products have been shown to be improve glycemic control in patients with type 2 diabetes.[61,81-83,85,90] However, there were no randomized studies found in the medical literature that directly compared the efficacy of the fixed-dose combination products to the coadministration of each component as separate formulations.

Thiazolidinediones may cause weight gain and fluid retention, as well as increase the risk for congestive heart failure and fractures.[1-6] The cardiovascular safety of rosiglitazone has been a controversial issue since 2007. The results of two cardiovascular outcomes studies with the thiazolidinediones have been reported (PROactive and RECORD); however, neither study directly compared pioglitazone and rosiglitazone.[19,25] A variety of meta-analyses have been conducted by independent investigators to assess the link between the use of thiazolidinediones and cardiovascular events.[26-33] Currently, the prescribing information for pioglitazone and rosiglitazone differ with regards to myocardial ischemic events; however, other safety issues are similar.[1-6] In contrast to pioglitazone, rosiglitazone-containing products are associated with a boxed warning regarding an increased risk of myocardial infarction. Because of the observed adverse cardiovascular outcomes, rosiglitazone-containing products are FDA-approved for the management of type 2 diabetes after consultation with a healthcare professional who has considered and advised the patient of the risks and benefits of therapy. Furthermore, use of rosiglitazone-containing products in patients not already receiving the agent is appropriate for patients who have decided not to take pioglitazone due to medical reasons. Due to the potential increased risk of myocardial infarction, rosiglitazone is available only through a restricted distribution program called the AVANDIA-Rosiglitazone Medicines Access Program.[2]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the thiazolidinediones or any other antidiabetic drug.[1-6] Since these agents are not recommended as first-line therapy for the treatment of type 2 diabetes mellitus, the thiazolidinediones should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand pioglitazone-containing products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Rosiglitazone-containing products have a clinical disadvantage compared to the other brands, generics and OTC products in the class (if applicable).

## XI. Recommendations

No brand pioglitazone-containing product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Rosiglitazone-containing products should not be placed in preferred status regardless of cost.

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Antidiabetic Agents, Miscellaneous
# AHFS Class 682092
# November 14, 2012

## I. Overview

Mifepristone (Korlym®) is classified as a antidiabetic agent, miscellaneous by the American Hospital Formulary Service. Mifepristone is a cortisol receptor blocker Food and Drug Administration (FDA)-approved to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery.[1] Mifepristone is the first and only approved medication for Cushing's syndrome patients and has been designated as an Orphan Drug by the FDA for this indication.[2] When administered in high doses, mifepristone is a selective antagonist of the GR-II glucocorticoid receptor and blocks the effects of cortisol. Mifepristone and the three active metabolites have a greater affinity for the glucocorticoid receptor compared to dexamethasone and cortisol, and have little to no affinity for estrogen, muscarinic, histaminic, or monoamine receptors. Of note, mifepristone does not reduce cortisol levels.[1,3]

Excess cortisol production, the biochemical hallmark of endogenous Cushing's syndrome, may be caused by either excess adrenocorticotropic hormone secretion (from a pituitary or other ectopic tumor) or independent adrenal overproduction of cortisol. Clinical features of Cushing's syndrome typically reflect prolonged and inappropriately high exposure to glucocorticoids, including weight gain, severe fatigue and muscle weakness, high blood pressure, depression, cognitive impairment, purplish skin striae, easy bruising, loss of libido, diabetes, hirsutism, acne and mental disorders.[4,5] Medical therapies may have a primary or adjunctive role in some patients. In patients in whom surgery has failed to control the disease, medical management is essential to reduce or normalize hypercortisolemia, and should be utilized prior to considering bilateral adrenalectomy. Medical therapies consist of adrenolytic agents (ketoconazole, metyrapone, aminoglutethimide [not available in the United States], mitotane, etomidate) and neuromodulatory agents (somatostatin analogs, dopamine agonists, peroxisome proliferator-activated receptor-γ agonists, retinoic acid and glucocorticoid receptor antagonists).[4-6] Adrenolytic agents typically work to decrease cortisol levels and are the most widely used agents. In particular, among patients with hypercortisolism in whom medical therapy is indicated, ketoconazole is considered first-line therapy.[6] The safety and efficacy of neuromodulatory therapies in endogenous Cushing's syndrome are still being evaluated.[5]

At lower doses mifepristone is a selective antagonist of the progesterone receptor.[1] The agent is also available as the branded agent Mifeprex®, which is FDA-approved for the medical termination of intrauterine pregnancy through 49 days' of pregnancy.[7]

The antidiabetic agents, miscellaneous that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Currently Mifepristone (Korlym®) is the only agent in the class and although the class has been reviewed previously this is the first review of Mifepristone (Korlym®).

**Table 1. Antidiabetic Agents, Miscellaneous Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Mifepristone | tablet | Korlym® | none |

PDL=Preferred Drug List

## II. Evidence-Based Medicine and Current Treatment Guidelines

No clinical guidelines regarding the treatment of Cushing's syndrome were identified.

## III. Indications

The Food and Drug Administration (FDA)-approved indication for mifepristone is noted in Table 2. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

**Table 2. FDA-Approved Indications for Antidiabetic Agents, Miscellaneous[1]**

| Indication | Mifepristone |
|---|---|
| Control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed or who are not candidates for surgery | ✔ |

## IV. Pharmacokinetics

The pharmacokinetic parameters of the antidiabetic agents, miscellaneous are listed in Table 3.

**Table 3. Pharmacokinetic Parameters of Antidiabetic Agents, Miscellaneous[1,3]**

| Generic Name(s) | Bioavailability (%) | Protein Binding (%) | Metabolism (%) | Half-Life (hours) |
|---|---|---|---|---|
| Mifepristone | 69 | 99 | Liver (extensive, % not reported) | 20 to 85 |

## V. Drug Interactions

Due to the long serum half-life of mifepristone, at least two weeks should elapse after cessation of mifepristone before initiating or increasing the dose of any interacting concomitant medication.[1]

Discontinuation or dose reduction of drugs whose metabolism is largely or solely mediated by cytochrome P450 (CYP) 3A may be necessary with mifepristone coadministration. Other drugs with similar high first pass metabolism in which CYP3A is the primary route of metabolism should be used with extreme caution if co-administered with mifepristone.[1]

Medications that inhibit CYP3A could increase plasma mifepristone concentrations and dose reduction of mifepristone may be required. Avoid coadministration of mifepristone and CYP3A inducers.[1]

When given concomitantly with mifepristone, drugs that are substrates of CYP2C8/2C9 should be used at the smallest recommended doses, and patients should be closely monitored for adverse events.[1]

The concomitant use of bupropion and efavirenz should be undertaken with caution.[1]

Mifepristone is a progesterone-receptor antagonist and will interfere with the effectiveness of hormonal contraceptives; therefore, non-hormonal contraceptive methods should be used.[1]

## VI. Adverse Drug Events

The most common adverse drug events reported with the antidiabetic agents, miscellaneous are listed in Table 4. The boxed warning for mifepristone is listed in Table 5.

**Table 4. Adverse Drug Events (%) Reported with Antidiabetic Agents, Miscellaneous[1,3]**

| Adverse Event | Mifepristone |
|---|---|
| **Gastrointestinal** | |
| Constipation | 10 |
| Diarrhea | 12 |

| Adverse Event | Mifepristone |
|---|---|
| Dry mouth | 18 |
| Nausea | 48 |
| Vomiting | 26 |
| **General Disorders and Administration/Site Conditions** | |
| Edema peripheral | 26 |
| Fatigue | 48 |
| Pain | 14 |
| **Infections and Infestations** | |
| Nasopharyngitis | 12 |
| Sinusitis | 14 |
| **Investigations** | |
| Blood potassium decreased | 34 |
| Thyroid function test abnormal | 18 |
| **Metabolism and Nutrition Disorders** | |
| Anorexia | 10 |
| Decreased appetite | 20 |
| **Musculoskeletal and Connective Tissue Disorders** | |
| Arthralgia | 30 |
| Back pain | 16 |
| Myalgia | 14 |
| Pain in extremity | 12 |
| **Nervous System** | |
| Dizziness | 22 |
| Headache | 44 |
| Somnolence | 10 |
| **Psychiatric Disorders** | |
| Anxiety | 10 |
| **Reproductive System and Breast Disorders** | |
| Endometrial hypertrophy | 38* |
| **Respiratory, Thoracic, and Mediastinal Disorders** | |
| Dyspnea | 16 |
| **Vascular Disorders** | |
| Hypertension | 24 |

*The denominator was 26 females who had baseline and end-of-trial transvaginal ultrasound.
✓ Percent not specified.

**Table 5. Boxed Warning for Korlym® (mifepristone)[1]**

| WARNING |
|---|
| Mifepristone is a potent antagonist of progesterone and cortisol via the progesterone and glucocorticoid (GR-II) receptors, respectively. The antiprogestational effects will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with mifepristone and prevented during treatment and for one month after stopping treatment by the use of a non-hormonal medically acceptable method of contraception unless the patient has had a surgical sterilization, in which case no additional contraception is needed. Pregnancy must also be excluded if treatment is interrupted for more than 14 days in females of reproductive potential. |

## VII. Dosing and Administration

The usual dosing regimen for the antidiabetic agents, miscellaneous are listed in Table 6.

**Table 6. Usual Dosing Regimens for Antidiabetic Agents, Miscellaneous[1,3]**

| Generic Name | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| Mifepristone | Control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery: Tablet: initial, 300 mg QD; maximum, 1,200 mg QD or 20 mg/kg/day | Safety and efficacy in pediatric patients have not been established. | Tablet: 300 mg |

QD=once daily

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antidiabetic agents, miscellaneous are summarized in Table 7.

**Table 7. Comparative Clinical Trials with Antidiabetic Agents, Miscellaneous**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Fleseriu et al.[8] (2012)<br><br>Mifepristone 300 to 1,200 mg QD<br><br>Patients started with 300 mg QD and if no significant clinical improvement, doses could be increased to 600 mg QD on day 14, 900 mg QD at week 6 and 1,200 mg QD at week 10. | MC, OL<br><br>Adults with confirmed endogenous CS with type 2 diabetes mellitus, impaired glucose tolerance, or a diagnosis of hypertension in addition to ≥2 of the following symptoms: Cushingoid appearance (moon facies, dorsocervical fat pad, and plethora), increased body weight or central obesity, proximal muscle weakness, low bone mineral density (T score <-1.0), psychiatric symptoms, and skin changes (hirsutism, violaceous striae, or acne) | N=50<br><br>24 weeks | Primary:<br>Change ≥25% in $AUC_{glucose}$ on oGTT from baseline (for patients with CS and type 2 diabetes mellitus or impaired glucose tolerance [C-DM cohort]) and change ≥5 mm Hg in DBP from baseline to week 24 (for patients with hypertension [C-HT cohort])<br><br>Secondary:<br>Changes in glucose homeostasis, BP, lipids, weight, body composition change, clinical appearance, strength, neuropsychological and quality of life parameters and safety | Primary:<br>In the C-DM mITT population, the $AUC_{glucose}$ was reduced by ≥25% on oGTT in 60% (15/25) of patients receiving mifepristone compared to baseline (P<0.001).<br><br>In the C-HT mITT treatment group, 38.1% (8/21) of patients treated with mifepristone achieved ≥5 mm Hg decline in DBP compared to baseline (P<0.05).<br><br>Secondary:<br>Overall, the clinical responder rate was 87% at week 24 compared to baseline (P<0.0001). Specifically, 92% of patients in the C-DM group and 81% of those in the C-HT group achieved a median clinical improvement score of +1 (P values not reported).<br><br>Overall, FPG decreased from 149.0±74.7 mg/dL at baseline to 104.7±37.5 mg/dL after 24 weeks (P<0.03). In the C-DM group, 72% of patients achieved ≥25% reduction from baseline in $AUC_{glucose}$ or a reduction in antidiabetic medication (95% CI, 50.6 to 87.9). The mean $HbA_{1c}$ was significantly reduced from baseline following mifepristone treatment (6.29±0.99 vs 7.43±1.52%; P<0.001). Of the 12 patients with an $HbA_{1c}$ >7.0% at baseline, nine were able to lover their $HbA_{1c}$ below 7.0%, including six reaching an $HbA_{1c}$ 6.0% or below. Patients in both the C-DM and C-HT treatment groups who were insulin resistant at baseline demonstrated rapid and significant improvements in $AUC_{insulin}$, which continued throughout the study. Insulin sensitivity was improved as evident by changes in HOMA-IR.<br><br>In the mITT group, the mean±SD change in bodyweight from baseline to week 24 following mifepristone treatment was -5.7±7.4% (P<0.001). Overall, 24 mifepristone-treated patients lost ≥5% of their baseline weight, and 10 patients lost ≥10%. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Mifepristone treatment was associated with a statistically significant reduction in waist circumference in women (-6.8±5.8 cm; P<0.001) and men (-8.4±5.9 cm; P<0.001).<br><br>At week 24, the mean total body fat declined by 3.6% (P<0.001), absolute fat mass declined by 13.9% (P<0.001), total body of the trunk declined by 15.6% (P<0.001) and by 17.1% (P<0.001) for the abdominal region.<br><br>Overall, 52.5% of patients with hypertension at baseline had either a response in DBP or a reduction in antihypertensive medication use. There were no statistically significant differences in mean SBP and DBP from baseline after 24 weeks of treatment in C-HT patients (129.5±16.3/82.9±11.4 vs 129.9±19.0/82.8±13.2 mm Hg) or in C-DM patients who also had hypertension (137.7±24.0/86.4±15.3 vs 132.2±16.7/82.4±13.2 mm Hg).<br><br>There were statistically significant improvements in the median BDI-II depression scores in the mITT population (P<0.001). For patients with at least mild depression at baseline, (BDI-II >14), the median score improved from 23 to 12 at 24 weeks (P<0.001). Similarly, improvements in cognition scores were also reported (P<0.01). Patients treated with mifepristone experienced statistically significant improvements in quality of life scores at 24 weeks compared to baseline in both mental (P=0.01) and physical (P=0.02) composite scores.<br><br>Adverse events occurred in 88% of mifepristone-treated patients, with the most common being nausea (48%), fatigue (48%), headache (44%), decreased blood potassium (34%), arthralgia (30%), vomiting (26%), peripheral edema (26%), hypertension (24%), dizziness (22%), decreased appetite (20%), and endometrial thickening (20%). Seven patients discontinued mifepristone due to adverse events. |

Drug regimen abbreviations: QD=once daily
Study abbreviations: CI=confidence interval, MC=multicenter, OL=open label
Miscellaneous abbreviation: $AUC_{glucose}$=area under the curve for glucose, $AUC_{insulin}$= area under the curve for insulin, BDI-II-Beck depression inventory, BP=blood pressure, CS=Cushing's syndrome, DBP=diastolic blood pressure, FPG=fasting plasma glucose, $HbA_{1c}$=glycosylated hemoglobin $A_{1c}$, HOMA-IR=homeostatic model assessment of insulin resistance, mITT=modified intent to treat, oGTT=oral glucose tolerance test, QOL=quality of life, SBP=systolic blood pressure, SD=standard deviation

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 8. Relative Cost of Antidiabetic Agents, Miscellaneous**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Mifepristone | tablet | Korlym® | $$$$$ | N/A |

N/A=Not available

## X. Conclusions

Mifepristone is the first agent Food and Drug Administration (FDA)-approved for the management of Cushing's syndrome.[1,2] Specifically, mifepristone is a cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance and have failed surgery or are not candidates for surgery. Mifepristone should not be used for the treatment of type 2 diabetes unrelated to endogenous Cushing's syndrome.[1] Mifepristone has been designated as an Orphan Drug for the treatment of the clinical manifestations of endogenous Cushing's syndrome by the FDA.[2]

There is an overall lack of guidance within published literature and clinical guidelines as to the role of mifepristone in the management of endogenous Cushing's syndrome. Following 24 weeks of treatment with mifepristone in patients with Cushing's syndrome, there were reductions in glucose area under the curve and reductions in diastolic blood pressure in adult patients with type 2 diabetes, glucose tolerance or hypertension.[7] Patients receiving mifepristone have also demonstrated varying degrees of improvement in Cushing's syndrome manifestations; however, it is not clear as to whether these changes are a result of mifepristone treatment.[7]

Based on the mechanism of action of mifepristone and its approved indication, the agent can only be used in certain patients with endogenous Cushing's syndrome and there is potential for it to be used in combination with

other established treatments. Cushing's syndrome treatment goals include the reversal of clinical features, the normalization of biochemical changes with minimal morbidity, and long-term control without recurrence. Optimal treatment is surgical resection by selective adenomectomy, with second-line options that include repeated pituitary surgery, radiotherapy, or bilateral adrenalectomy.[5] Medical therapy plays an essential role in patients in whom surgery has failed to control the disease to reduce or normalize hypercortisolemia. Currently, adrenolytic therapies (ketoconazole, metyrapone, aminoglutethimide [not available in the United States], mitotane, etomidate) are the most widely utilized agents, with fluconazole considered first-line to treat hypercortisolism. The safety and efficacy of neuromodulatory therapies (somatostatin analogs, dopamine agonists, peroxisome proliferator-activated receptor-γ agonists, retinoic acid, glucocorticoid receptor antagonists) in Cushing's syndrome have not been established .[4,5]

There is insufficient evidence to support that one brand antidiabetic agent, miscellaneous is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand antidiabetic agent, miscellaneous is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

## XII. References

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# Alabama Medicaid Agency
# Pharmacy and Therapeutics Committee Meeting
# Pharmacotherapy Review of Multivitamin Preparations: Prenatal Vitamins
# AHFS Class 882800
# November 14, 2012

## I. Overview

Women of reproductive age should maintain good nutritional status prior to, during and after pregnancy to minimize health risks to both the mother and child. This includes maintaining a healthy weight, participating in physical activity, consuming a variety of foods to meet the Dietary Reference Intake recommendations, as well as appropriate and timely supplementation with multivitamins.[1-3] There are several organizations that have published dietary guidelines for the perinatal period (preconception, pregnancy and during lactation).[4,5] However, most women of childbearing age do not maintain a healthy diet and do not consume enough vitamins (A, C, B-6 and E), calcium, folic acid, iron, magnesium or zinc.[1,2]

Women have an increased requirement for certain nutrients during pregnancy, including folate and iron. Folate is necessary for deoxyribonucleic acid (DNA) synthesis and cell division, and is an important nutrient prior to and during pregnancy. Many studies have shown that folic acid supplementation is associated with a lower risk of neural tube defects, which are serious birth defects of the spine and brain.[1-11] The American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), American Dietetic Association (ADA), Centers for Disease Control and Prevention (CDC), and the United States Preventive Services Task Force (USPSTF) all recommend that women of reproductive age consume folic acid on a daily basis.[1,7-11] The amount of folic acid that is recommended varies slightly among the organizations; however, the most recent publication by the USPSTF recommends that all women planning pregnancy take a supplement containing 400 to 800 µg of folic acid on a daily basis.[8] A higher dose of folic acid (4 mg/day) is recommended for women who have had a previous pregnancy affected by a neural tube defect, which should begin one to three months prior to conception and continue throughout the first trimester of pregnancy.[2,8-9,11]

Iron deficiency is common in women of childbearing age due to menstruation, insufficient dietary intake and multiple pregnancies.[2] There is an increase in iron requirements during pregnancy due to the expansion of blood volume and red blood cell mass.[12] Iron deficiency anemia during pregnancy can lead to fetal complications such as premature delivery, intrauterine growth restrictions and neonatal mortality.[2,12] It is recommended that women consume 27 mg of elemental iron per day during pregnancy.[5] Pregnant women should be screened for iron deficiency anemia, and if present, be treated with supplemental iron (60 to 120 mg/day).[1-3,12]

There is evidence that maternal consumption of folic acid-containing multivitamins may reduce the risk of neural tube defects, cardiac defects, urinary tract defects, limb defects, as well as other birth defects.[2,13] The ADA recommends supplementation with a multivitamin for pregnant women with iron deficiency anemia, poor-quality diets, those who consume no or small amounts of animal source foods, women carrying two or more fetuses, those who smoke or abuse alcohol or drugs, and for women who are infected with human immunodeficiency virus.[1] In addition to a well-balanced diet, supplementation with a folic acid-containing multivitamin should be encouraged in all women of reproductive age to help support healthy pregnancy outcomes.[2]

There is a wide variety of prenatal vitamins currently available. Most of the preparations contain folic acid and iron; however, the amount varies among the products (refer to the dosing and administration section for comparison). The products also contain various combinations and quantities of vitamins and minerals. Additional nutrients which may be added to a prenatal vitamin include aspartame, docusate, L-methylfolate, omega-3 fatty acids and omega-6 fatty acids. Folic acid must be broken down to L-methylfolate to be used at the cellular level; however, some individuals are unable to convert folic acid to its active form. Some of the prenatal formulations contain L-methylfolate for women who are unable to fully metabolize folic acid. Omega-3 fatty acids include α-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Omega-3 and omega-6 fatty acids must be obtained from food because the human body cannot synthesize these nutrients. DHA and EPA can be synthesized de novo from ALA; however, intake of ALA has not been shown to increase maternal, fetal or

breast milk DHA levels.[2-3] Both DHA and EPA are considered essential fatty acids which are necessary for nervous tissue growth and function.[14] Some studies suggest that they may play a role in fetal/neonatal visual and neural growth when taken during pregnancy, as well as help prevent low birth weight. There are recommended DRIs that have been established for ALA; however, it is unclear how much DHA or EPA a pregnant woman should consume through her diet and via supplementation.[2-3,15]

The prenatal vitamins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. It should be noted that the products included in this review contain an extensive ingredient list, which can be found separately in the prescribing information. The term "prenatal vitamins" in Table 1 collectively refers to all of the active vitamin and mineral ingredients. Additional ingredients, including folic acid and iron, have been listed out separately. Many of the prenatal vitamins are available in a generic formulation, including products which contain omega-3 fatty acids. The last time this class was reviewed was November 2009.

**Table 1. Prenatal Vitamins Included in this Review**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Iron, folic acid, multivitamins with minerals | Tablet | OB Complete®* | iron, folic acid, multivitamins with minerals |
| Prenatal vitamins | Capsule | Vinate IC®† | none |
| Prenatal vitamins, iron, folic acid | Capsule, chewable tablet, tablet | Concept OB®*, Maxinate®†, Natafort®, Natalvit®†, Nestabs®*, OB-Complete Premier®, Prefera OB®, Prenata®, Select-OB®, Tricare®, Vinate II®, Vinate AZ®†, Vinate Care®*, Vinate One®*, Vitafol-OB®, Vitafol-PN®, Viva CT® | prenatal vitamins, iron, folic acid |
| Prenatal vitamins, iron, omega-3 fatty acids | Combination package | Bal-Care DHA Essential®† | none |
| Prenatal vitamins, iron, folic acid, DHA | Capsule, combination package | Gesticare DHA®, Natelle One®, Nestabs DHA®*, OB Complete®, Paire OB Plus DHA®, Prefera-OB One®, Reaphirm®*, Select-OB+DHA®*, Vitafol-OB+DHA®, Vitafol-One®*, Vitafol-Plus® | prenatal vitamins, iron, folic acid, DHA |
| Prenatal vitamins, iron, folic acid, docusate | Tablet | Citranatal RX®*, Vinacal®*, Vinate Calcium®, Vinate GT®*, Vinate PN Care®, Vinate Ultra®*† | prenatal vitamins, iron, folic acid, docusate |
| Prenatal vitamins, iron, folic acid, L-methylfolate† | Tablet | N/A | prenatal vitamins, iron, folic acid, L-methylfolate† |
| Prenatal vitamins, iron, folic acid, omega-3 fatty acids | Capsule, combination package | Concept DHA®*, Duet DHA Complete®*, Duet DHA Balanced®*, OB Complete With DHA®, OB-Natal One®*†, PR Natal 400®*, PR Natal 430®*, PR Natal 400 EC®, PR Natal 430 EC®, Viva DHA®*† | prenatal vitamins, iron, folic acid, omega-3 fatty acids |

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Current PDL Agent(s) |
|---|---|---|---|
| Prenatal vitamins, iron, folic acid, selenium | Tablet | Vinate-M®* | prenatal vitamins, iron, folic acid, selenium |
| Prenatal vitamins, iron, folic acid, vitamin B6 | Tablet | Citranatal B-Calm®* | prenatal vitamins, iron, folic acid, vitamin B6 |
| Prenatal vitamins, iron, folic acid, DHA, docusate | Capsule, combination package | Citranatal 90 DHA®, Citranatal Assure®, Citranatal DHA®*, Citranatal Harmony®*, Nexa Select®*, Prenexa®* | prenatal vitamins, iron, folic acid, DHA, docusate |
| Prenatal vitamins, iron, folic acid, DHA, fish oil | Capsule | OB Complete 400®, OB Complete One® | none |
| Prenatal vitamins, iron, folic acid, DHA, L-methylfolate† | Capsule | N/A | prenatal vitamins, iron, folic acid, DHA, L-methylfolate |
| Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids | Combination package | Prefera-OB Plus DHA® | none |
| Prenatal vitamins, iron, folic acid, DHA, ubidecarenone† | Tablet | N/A | prenatal vitamins, iron, folic acid, DHA, ubidecarenone |
| Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone | Tablet | Preque 10® | none |
| Prenatal vitamins, iron, folic acid, DHA, EPA, fish oil | Capsule | Elite-OB 400®* | prenatal vitamins, iron, folic acid, DHA, EPA, fish oil |
| Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil | Capsule | Tricare Prenatal DHA One® | none |

*Generic is available in at least one dosage form or strength.
†Clinical information for this product is not available in the various drug databases.
DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid
N/A=Not available

## II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the prenatal vitamins are summarized in Table 2. The recommended Dietary Reference Intakes for women are listed in Table 3.

**Table 2. Treatment Guidelines Using the Prenatal Vitamins**

| Clinical Guideline | Recommendation(s) |
|---|---|
| United States Preventive Services Task Force: **Folic Acid for the Prevention of Neural Tube Defects: United States Preventive Services Task Force Recommendation Statement[8] (2009)** | • All women planning or capable of pregnancy should take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid.<br>• This recommendation applies to women who are planning or capable of pregnancy, but it does not apply to women who have had a previous pregnancy affected by neural tube defects or women taking certain antiseizure medicines. Most organizations recommend that these women take higher doses of folic acid.<br>• Most studies indicate the need to start folic acid supplementation at least one month before conception and to continue daily supplements through the first two to three months of pregnancy. Studies also indicate that 50% of pregnancies in the United States are unplanned, and clinicians should therefore advise all women who are capable of pregnancy to take folic acid supplements. |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | • Good evidence from randomized trials in settings without fortification of food suggests that a multivitamin with 0.8 mg (800 µg) of folic acid reduces the risk for neural tube defects. Observational studies done before fortification report a reduction of neural tube defects in women taking a supplement with 0.4 mg (400 µg) of folic acid (the generally available dose). Evidence indicates that most women in the United States are not ingesting fortified foods at a level thought to provide optimal benefit. In a setting in which food is fortified with folic acid, the effective amount of additional folic acid supplementation is unclear. |
| Position of the American Dietetic Association: **Nutrition and Lifestyle for a Healthy Pregnancy Outcome[1] (2008)** | • Women of childbearing age should maintain good nutritional status through a lifestyle that optimizes maternal health and reduces the risk of birth defects, suboptimal fetal development, and chronic health problems in their children.<br>• The key components of a health-promoting lifestyle during pregnancy include appropriate weight gain; appropriate physical activity; consumption of a variety of foods in accordance with the Dietary Guidelines for Americans 2005; appropriate and timely vitamin and mineral supplementation; avoidance of alcohol, tobacco and other harmful substances; and safe food handling.<br>• Pregnant women should consume 600 µg of synthetic folic acid daily from fortified foods or supplements in addition to food forms of folate in a varied diet. This can reduce the risk of neural tube defects if taken prior to conception through the sixth week of pregnancy, and possibly reduces other birth defects if taken later in pregnancy.<br>• Maternal iron deficiency anemia increases the risk of low birth weight and possibly preterm delivery and perinatal mortality, and may impair maternal-infant interaction. Supplementation with 27 mg of iron daily during pregnancy is recommended. Anemic women may need 60 mg daily until the anemia is resolved.<br>• In pregnancy, low vitamin D levels lead to low serum calcium in the infant and adversely affects neonatal bone metabolism (in more severe cases). Supplementation of pregnant women with amounts greater than the Recommended Dietary Allowance of 200 IU daily does not appear to provide additional benefit.<br>• Multivitamin and mineral supplements are recommended for women with iron deficiency anemia or poor-quality diets and for those who consume no or small amounts of animal source foods. For vegans and even some lacto-ovo vegetarians, supplemental vitamin B-12 is particularly important during both pregnancy and lactation to transfer enough to the fetus and infant to avoid developmental delays. Women carrying two or more fetuses, and those who smoke or abuse alcohol or drugs, should also take a multivitamin and mineral supplement. Multivitamin supplements may also be beneficial in pregnant women who are infected with human immunodeficiency virus (HIV). |
| The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: **Anemia in Pregnancy[12] (2008)** | • All pregnant women should be screened for anemia during pregnancy. Those with iron deficiency anemia should be treated with supplemental iron, in addition to prenatal vitamins. Patients with anemia other than iron deficiency anemia should be further evaluated.<br>• Iron deficiency anemia during pregnancy has been associated with an increased risk of low birth weight, preterm delivery, and perinatal mortality.<br>• Severe anemia with maternal hemoglobin levels <6 g/dL has been associated with abnormal fetal oxygenation resulting in nonreassuring fetal heart rate patterns, reduced amniotic fluid volume, fetal cerebral vasodilatation, and fetal death. Thus, maternal transfusion should be |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | considered for fetal indications.<br>• Iron supplementation decreases the prevalence of maternal anemia at delivery. However, it is unclear whether iron supplementation in well-nourished pregnant women who are not anemic affects perinatal outcomes.<br>• There is little evidence that iron supplementation results in morbidity beyond gastrointestinal symptoms, except in patients with hemochromatosis or certain other genetic disorders. |
| American Academy of Family Physicians (AAFP):<br>**Clinical Preventative Services: Neural Tube Defects[11] (2009)** | • It is recommended that all women planning or capable of pregnancy take a daily supplement containing 0.43 to 0.8 mg (400 to 800 µg) of folic acid. |
| Centers for Disease Control and Prevention:<br>**Recommendations to Improve Preconception Health and Health Care-United States[7] (2006)** | Preconception risk factors for adverse pregnancy outcomes<br>• Alcohol misuse<br>  ○ It is not safe to drink alcohol at any time during pregnancy, and harm can occur early, before a woman realizes that she is or might be pregnant. Fetal alcohol syndrome and other alcohol-related birth defects can be prevented if women stop drinking alcohol before conception.<br>• Anti-epileptic drugs<br>  ○ Certain anti-epileptic drugs (e.g., valproic acid) are known teratogens. Recommendations suggest that women who are on a regimen of these drugs and who are contemplating pregnancy should be prescribed a lower dosage of these drugs.<br>• Diabetes (preconception)<br>  ○ The threefold increase in the prevalence of birth defects among infants of women with type 1 and type 2 diabetes is substantially reduced through proper management of diabetes.<br>• Folic acid<br>  ○ Daily use of vitamin supplements containing folic acid has been shown to reduce the occurrence of neural tube defects by as much as two thirds.<br>• Hepatitis B<br>  ○ Vaccination is recommended for men and women who are at risk for acquiring hepatitis B virus (HBV) infection. Preventing HBV infection in women of childbearing age prevents transmission of infection to infants and eliminates risks to the women of HBV infection and sequelae, including hepatic failure, liver carcinoma, cirrhosis, and death.<br>• HIV/acquired immune deficiency syndrome<br>  ○ If HIV infection is identified before conception, timely antiretroviral treatment can be administered, and women (or couples) can be given additional information to help prevent mother-to-child transmission.<br>• Hypothyroidism<br>  ○ The dosages of thyroxine (e.g., levothyroxine) need to be adjusted for proper neurologic development of the fetus.<br>• Isotretinoins<br>  ○ Use of isotretinoins (e.g., Accutane®) to treat acne during pregnancy can result in miscarriage and birth defects. Effective pregnancy prevention should be implemented to avoid unintended pregnancies among women with childbearing potential who use this medication.<br>• Maternal phenylketonuria |

| Clinical Guideline | Recommendation(s) |
|---|---|
| | ○ Women diagnosed with maternal phenylketonuria as infants have an increased risk for delivering infants with mental retardation or birth defects. However, this adverse outcome can be prevented when mothers adhere to a low-phenylalanine diet before conception and continue it throughout their pregnancy.<br>• Rubella seronegativity<br>○ Rubella vaccination provides protective seropositivity and prevents congenital rubella syndrome.<br>• Obesity<br>○ Adverse perinatal outcomes associated with maternal obesity include neural tube defects, preterm delivery, diabetes, cesarean delivery, and hypertensive and thromboembolic disease. Appropriate weight loss and nutritional intake before pregnancy reduces these risks. |
| The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: **Neural Tube Defects[9] (2003)** | • Periconceptional folic acid supplementation is recommended because it has been shown to reduce the occurrence and recurrence of neural tube defects.<br>• For low-risk women, folic acid supplementation of 400 µg per day currently is recommended because nutritional sources alone are insufficient. Higher levels of supplementation should not be achieved by taking excess multivitamins because of the risk of vitamin A toxicity.<br>• The ideal dose for folic acid supplementation has not been appropriately evaluated in prospective clinical studies. A 400 µg supplement currently is recommended for women capable of becoming pregnant.<br>• For women at high risk of neural tube defects or who have had a previous pregnancy with a neural tube defect, folic acid supplementation of 4 mg per day is recommended. |
| American Academy of Pediatrics: **Folic Acid for the Prevention of Neural Tube Defects[10] (1999)** | • The American Academy of Pediatrics (AAP) endorses the United States Preventive Services Task Force recommendation that all women of childbearing age who are capable of becoming pregnant should consume 400 (0.4 mg) µg of folic acid daily.<br>• Women with a history of a previous pregnancy resulting in a fetus with neural tube defects should be advised of the results of the MRC study. During times in which a pregnancy is not planned, these high-risk women should consume 4000 (4 mg) µg of folic acid per day. However, they should be offered treatment with 4000 µg of folic acid per day starting one month before the time they plan to become pregnant and throughout the first three months of pregnancy, unless contraindicated. Women should be advised not to attempt to achieve the 4000 µg daily dosage of folic acid by taking over-the-counter or prescription multivitamins containing folic acid because of the possibility of ingesting harmful levels of other vitamins, for example, Vitamin A. It should be noted that 4000 µg of folic acid did not prevent all neural tube defects in the MRC study. Therefore, high-risk patients should be cautioned that folic acid supplementation does not preclude the need for counseling or consideration of prenatal testing for neural tube defects. |

**Table 3. Dietary Reference Intake for Women[1,5,6]**

| Nutrient | Adult Women | Pregnancy | Lactation |
|---|---|---|---|
| Biotin | 25 to 30 µg | 30 µg | 35 µg |
| Folate | 400 µg DFE | 600 µg DFE | 500 µg DFE |

| Nutrient | Adult Women | Pregnancy | Lactation |
|---|---|---|---|
| Niacin | 14 mg | 18 mg | 17 mg |
| Pantothenic acid | 5 mg | 6 mg | 7 mg |
| Riboflavin | 1.0 to 1.1 mg | 1.4 mg | 1.6 mg |
| Thiamin | 1.0 to 1.1 mg | 1.4 mg | 1.4 mg |
| Vitamin A | 700 µg RAE | 750 to 770 µg RAE | 1,200 to 1,300 µg RAE |
| Vitamin $B_6$ | 1.2 to 1.3 mg | 1.9 mg | 2.0 mg |
| Vitamin $B_{12}$ | 2.4 µg | 2.6 µg | 2.8 µg |
| Vitamin C | 65 to 75 mg | 80 to 85 mg | 115 to 120 mg |
| Vitamin D | 5 µg | 5 µg | 5 µg |
| Vitamin E | 15 mg | 15 mg | 19 mg |
| Vitamin K | 75 to 90 µg | 75 to 90 µg | 75 to 90 µg |
| Calcium | 1,000 to 1,300 mg | 1,000 to 1,300 mg | 1,000 to 1,300 mg |
| Choline | 400 to 425 mg | 450 mg | 550 mg |
| Chromium | 24 to 25 µg | 29 to 30 µg | 44 to 45 µg |
| Copper | 890 to 900 µg | 1,000 µg | 1,300 µg |
| Fluoride | 3 mg | 3 mg | 3 mg |
| Iodine | 150 µg | 220 µg | 290 µg |
| Magnesium | 310 to 360 mg | 350 to 400 mg | 310 to 360 mg |
| Iron | 15 to 18 mg | 27 mg | 9 to 10 mg |
| Manganese | 1.6 to 1.8 mg | 2.0 mg | 2.6 mg |
| Molybdenum | 43 to 45 µg | 50 µg | 50 µg |
| Phosphorus | 700 to 1,250 mg | 700 to 1,250 mg | 700 to 1,250 mg |
| Selenium | 55 µg | 60 µg | 70 µg |
| Zinc | 8 to 9 mg | 11 to 12 mg | 12 to 13 mg |
| Alpha-linolenic acid | 1.1 g | 1.4 g | 1.3 g |
| Linoleic acid | 11 to 12 g | 13 g | 13 g |

DFE=dietary folate equivalents, RAE=retinol activity equivalents

## III. Indications

The Food and Drug Administration (FDA)-approved indications for the prenatal vitamins are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

**Table 4. FDA-Approved Indications for the Prenatal Vitamins[16-38]**

| Generic Name(s) | Nutritional Supplement for Use Prior to Conception, Throughout Pregnancy and During the Postnatal Period |
|---|---|
| Iron, folic acid, multivitamins with minerals | ✔ |
| Prenatal vitamins, iron, folic acid | ✔ |
| Prenatal vitamins, iron, folic acid, DHA | ✔ |
| Prenatal vitamins, iron, folic acid, docusate | ✔ |
| Prenatal vitamins, iron, folic acid, omega-3 fatty acids | ✔ |
| Prenatal vitamins, iron, folic acid, selenium | ✔ |
| Prenatal vitamins, iron, folic acid, vitamin B6 | ✔ |
| Prenatal vitamins, iron, folic acid, DHA, docusate | ✔ |
| Prenatal vitamins, iron, folic acid, DHA, fish oil | ✔ |
| Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids | ✔ |
| Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone | ✔ |
| Prenatal vitamins, iron, folic acid, DHA, EPA, fish oil | ✔ |

| Generic Name(s) | Nutritional Supplement for Use Prior to Conception, Throughout Pregnancy and During the Postnatal Period |
|---|---|
| Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil | ✔ |

DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid

## IV. Pharmacokinetics

There is limited or no data available on the pharmacokinetic properties of the prenatal vitamins.[16-38]

## V. Drug Interactions

There are no significant drug interactions reported with the prenatal vitamins.[16-38]

## VI. Adverse Drug Events

Adverse reactions with iron therapy may include anorexia, constipation, diarrhea, nausea, vomiting, dark stools and abdominal pain, which are usually transient. Allergic sensitization has been reported following both oral and parenteral administration of folic acid.[16-38] Accidental overdose of iron containing products is a leading cause of fatal poisoning in children under the age of six. The boxed warning for the prenatal vitamins is listed in Table 5.

**Table 5. Boxed Warning for the Prenatal Vitamins[16-38]**

| WARNING |
|---|
| Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of the reach of children. In case of accidental overdose, call a doctor or poison control center immediately. |

## VII. Dosing and Administration

The usual dosing regimens for the prenatal vitamins are listed in Table 6.

**Table 6. Usual Dosing Regimens for the Prenatal Vitamins[1638]**

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| Iron, folic acid, multivitamins with minerals | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Tablet:<br>50-1.25 mg |
| Prenatal vitamins | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>162-115.2-1 mg |
| Prenatal vitamins, iron, folic acid | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>85-1 mg<br><br>Chewable tablet:<br>29-1 mg<br>40-1 mg<br><br>Tablet:<br>20-0.8 mg<br>22-6-1 mg<br>27-1 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | | | 28-6-1 mg<br>29-1 mg<br>30-20-1 mg<br>32-1 mg<br>60-1 mg<br>65-1 mg<br>75-1 mg |
| Prenatal vitamins, iron, omega-3 fatty acids | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Combination package:<br>27-1-374 mg |
| Prenatal vitamins, iron, folic acid, DHA | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>22-6-1-200 mg<br>27-1-200 mg<br>28-1-250 mg<br>29-1-200 mg<br><br>Chewable tablet:<br>20-1-100 mg<br><br>Combination package:<br>27-1-250 mg<br>22-6-1-200 mg<br>29-1-200 mg<br>29-1-250 mg<br>32-1-230 mg<br>65-1-250 mg |
| Prenatal vitamins, iron, folic acid, docusate | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Tablet:<br>27-1-50 mg<br>30-50-1 mg<br>90-1-50 mg |
| Prenatal vitamins, iron, folic acid, L-methylfolate | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Tablet:<br>29-0.4-1.13 mg |
| Prenatal vitamins, iron, folic acid, omega-3 fatty acids | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>27-1-330 mg<br>28-1-200 mg<br>30-10-1-200 mg<br>35-1-200 mg<br><br>Combination package:<br>26-1-374 mg<br>27-1-300 mg<br>27-1-430 mg<br>29-1-400 mg<br>29-1-430 mg |
| Prenatal vitamins, iron, folic acid, selenium | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Tablet:<br>27 mg-1 mg-20 µg |
| Prenatal vitamins, iron, folic acid, vitamin B6 | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Tablet:<br>20-1-25 mg |
| Prenatal vitamins, iron, folic acid, DHA, docusate | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>27-1.25-55-300 mg<br>28-1-50-250 mg<br>29-1.25-55-325 mg<br>30-1-50-260 mg |

| Generic Name(s) | Usual Adult Dose | Usual Pediatric Dose | Availability |
|---|---|---|---|
| | | | Combination package:<br>27-1-50-250 mg<br>35-1-50-300 mg<br>90-1-50-300 mg |
| Prenatal vitamins, iron, folic acid, DHA, fish oil | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>40-10-1-300-476 mg<br>40-10-1-320-400 mg |
| Prenatal vitamins, iron, folic acid, DHA, L-methylfolate | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>27-0.4-1.13-250 mg |
| Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Combination package:<br>28-6-1-203 mg (200-0.5-2.5 mg) |
| Prenatal vitamins, iron, folic acid, DHA, ubidecarenone | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Tablet:<br>15-0.5-50-50 mg |
| Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Tablet:<br>15-0.5-25-50-50 mg |
| Prenatal vitamins, iron, folic acid, DHA, EPA, fish oil | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>35-5-1.2-44-320-40 mg |
| Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil | Administer once daily. | Safety and effectiveness have not been established in pediatric patients. | Capsule:<br>27-1-25-500 mg (215-45 mg) |

DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid

## VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the prenatal vitamins are summarized in Table 7. There were no studies found in the medical literature that directly compared the various prenatal vitamin preparations.

**Table 7. Comparative Clinical Trials with the Prenatal Vitamins**

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Gupta et al.[39] (2007)<br><br>Multivitamin supplementation plus folic acid 500 µg/day and iron 60 mg/day<br><br>vs<br><br>placebo plus supplementation with folic acid 500 µg/day and iron 60mg/day | DB, PC, RCT<br><br>Pregnant women between 24 to 32 weeks gestation with a BMI <18.5 and/or a hemoglobin level 7 to 9 g/dL | N=200<br><br>Median 52 to 58 days | Primary:<br>Birth weight, length, midarm, circumference, incidence of low birth weight, and early neonatal morbidity<br><br>Secondary:<br>Not reported | Primary<br>Infants in the micronutrient supplement group were 98 g heavier (95% CI, -16 to 213) and 0.8 cm longer (95% CI, 0.03 to 1.57) than infants born to mothers who received placebo.<br><br>Infants in the micronutrient supplement group were 0.2 cm larger in midarm circumference (95% CI, 0.04 to 0.36) than infants born to mothers who received placebo.<br><br>Incidence of low birth weight decreased from 43.1 to 16.2% in those infants whose mothers received micronutrient supplementation (RR, 0.3; 95% CI, 0.13 to 0.71; P=0.006) compared to infants whose mothers received placebo.<br><br>Early neonatal morbidity decreased from 28.0 to 14.8% in those infants whose mothers received micronutrient supplementation (RR, 0.42; 95% CI, 0.19 to 0.94; P=0.04) compared to infants whose mothers received placebo.<br><br>Women who were anemic were not likely to benefit more from multivitamin supplementation in terms of birth size.<br><br>There was no significant difference between birth size for women with hemoglobin levels of less than 9 g/dL and the rest in the micronutrient group.<br><br>Secondary:<br>Not reported |
| Haider et al.[40] (2006) | MA (9 RCTs)<br><br>Pregnant women | 15,378<br><br>Duration not | Primary:<br>Preterm birth, small for | Primary:<br>A significant decrease in the number of low birth weight babies was observed when comparing multiple micronutrient supplementation to |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Multiple micronutrient supplementation of 3 or more micronutrients<br><br>vs<br><br>placebo, no supplementation or supplementation with 2 or less micronutrients | (varying duration of pregnancies) | specified | gestational age, low birth weight, premature rupture of membranes, preeclampsia, miscarriage, maternal mortality, perinatal mortality<br><br>Secondary:<br>Maternal anemia | placebo, no supplementation or two or less micronutrients (RR, 0.83; 95% CI, 0.76 to 0.91).<br><br>No significant differences were observed in preterm birth and perinatal mortality (RR, 0.92; 95% CI, 0.82 to 1.04).<br><br>When multiple micronutrient supplementation was compared to iron and folic acid supplementation, no significant differences were observed in any primary outcome.<br><br>Secondary:<br>A significant decrease in maternal anemia was observed when comparing multiple micronutrient supplementation with placebo, no supplementation or supplementation of two or less micronutrients (RR, 0.61; 95% CI, 0.52 to 0.71).<br><br>No significant differences were observed in maternal anemia when multiple micronutrient supplementation was compared to iron and folic acid supplementation (RR, 1.23; 95% CI, 0.82 to 1.83). |
| Lumley et al.[41] (2000)<br><br>Multivitamins<br><br>vs<br><br>folate<br><br>vs<br><br>multivitamins plus folate | MA (4 RCTs)<br><br>Periconceptual women | N=6,425<br><br>Variable duration | Primary:<br>NTD<br><br>Secondary:<br>Not reported | Primary:<br>Periconceptional folate supplementation reduced the prevalence of neural tube defects (RR, 0.28; 95% CI, 0.13 to 0.58). The reduction is similar for the first occurrence of defects (RR, 0.07; 95% CI, 0.00 to 1.32) and for recurrent defects (RR, 0.31; 95% CI, 0.14 to 0.66). The number needed to treat for folate prevention of an NTD is 847.<br><br>The trials had very low power to identify differences in limb reduction defects (RR, 0.59; 95% CI 0.04 to 8.34), conotruncal defects (RR, 0.74; 95% CI, 0.16 to 3.32), orofacial clefts (RR, 0.76; 95% CI, 0.24 to 2.37) or all other major birth defects combined (RR, 0.76; 95% CI, 0.38 to 1.51).<br><br>Folate supplementation was not associated with an increase in conception (RR, 1.02; 95% CI 0.97 to 1.07).<br><br>No adverse effects of the folate supplementation were detected in terms of an increase in miscarriage (RR, 1.12; 95% CI, 0.98 to 1.29), or ectopic pregnancy (RR, 1.09; 95% CI, 0.47 to 2.55). There was no reduction in |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | stillbirths (RR, 0.78; 95% CI, 0.34 to 1.78).<br><br>There was no statistically significant reduction in NTD when multivitamins alone were compared with placebo (RR, 0.61; 95% CI, 0.26 to 1.45), when multivitamins were compared with multivitamins plus folate (RR, 2.05; 95% CI, 0.67 to 6.26), or when folate was compared with multivitamins plus folate (RR, 0.49; 95% CI, 0.09 to 2.66). When folate alone was compared with multivitamins alone there was a reduction with folate (RR, 0.27; 95% CI, 0.07 to 1.08), however this was not significant.<br><br>Secondary:<br>Not reported |
| Siega-Riz et al.[42] (2006)<br><br>Multivitamin supplementation containing 30 mg of elemental iron (ferrous sulfate)<br><br>vs<br><br>multivitamin supplementation without iron | RCT<br><br>Pregnant women who were less than 20 weeks of gestation with hemoglobin levels ≥110 g/L and ferritin levels ≥40 µg/L | N=429<br><br>>9 weeks | Primary:<br>Third trimester iron status, birth weight, preterm birth, and small-for-gestational age<br><br>Secondary:<br>Not reported | Primary:<br>There were no significant differences between the treatment groups in any of the iron status indicators measured.<br><br>Women who received iron supplementation gave birth to infants who weighed 108 g heavier than women who did not receive iron supplementation (P=0.03).<br><br>There were no significant differences among women who received iron supplementation compared to those who did not receive iron supplementation for the following outcomes: gestational age at delivery (P=0.43), low birth weight (4.8 vs 9.5%, respectively; P=0.09), preterm delivery (7.5 vs 13.9%, respectively; P=0.05), or small-for-gestational age (P=0.22).<br><br>Secondary:<br>Not reported |
| Goh et al.[43] (2006)<br><br>Prenatal multivitamin supplementation | MA (6RCTs)<br><br>Pregnant women | N=not specified<br><br>Variable duration | Primary:<br>Risk of pediatric cancer<br><br>Secondary:<br>Not reported | Primary:<br>Use of prenatal multivitamins by the pregnant mothers was associated with a protective effect for childhood leukemia (OR, 0.64; 95% CI 0.53 to 0.78).<br><br>Ingestion of prenatal multivitamins was associated with a protective effect for acute lymphoblastic leukemia (OR, 0.61; 95% CI, 0.50 to 0.74). |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | There was only one study that reported information regarding acute myeloid leukemia which suggested a protective effect of prenatal multivitamin use.<br><br>Supplementation with prenatal vitamins was associated with a decreased risk for neuroblastoma (OR, 0.53; 95% CI, 0.42 to 0.68).<br><br>Prenatal supplementation was associated with decreased risk for pediatric brain tumors (OR, 0.73; 95% CI, 0.60 to 0.88)<br><br>Secondary:<br>Not reported |
| Hofmeyr et al.[44] (2006)<br><br>Calcium supplementation (1.5 to 2 g/day)<br><br>vs<br><br>placebo | MA (12 RCTs)<br><br>Pregnant women | N=15,206<br><br>Variable duration | Primary:<br>Hypertensive disorders of pregnancy and related maternal and child outcomes<br><br>Secondary:<br>Not reported | Primary:<br>There was less high blood pressure with calcium supplementation rather than placebo (RR, 0.70; 95% CI, 0.57 to 0.86).<br><br>There was a reduction in the risk of pre-eclampsia (RR, 0.48; 95% CI, 0.33 to 0.69).<br><br>The relative risk of having the composite outcome maternal death or serious morbidity was reduced for women allocated calcium supplementation compared with placebo (RR, 0.80; 95% CI, 0.65 to 0.97).<br><br>There was no difference in the rate of placental abruption between the groups (RR, 0.86; 95% CI, 0.55 to 1.34).<br><br>There was no significant effect on the relative risk of caesarean section (RR, 0.95; 95% CI, 0.88 to 1.01).<br><br>There was no overall difference in proteinuria between groups (RR, 1.04; 95% CI, 0.86 to 1.26).<br><br>There was no difference in the rate of severe pre-eclampsia (RR, 0.74; 95% CI, 0.48 to 1.15) or eclampsia between the groups (RR, 0.73; 95% CI, 0.41 to 1.27).<br><br>There was no difference in maternal deaths between the groups (RR, 0.17; |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
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| | | | | 95% CI, 0.02 to 1.39).<br><br>There was no overall effect on preterm birth (RR, 0.81; 95% CI, 0.64 to 1.03).<br><br>There was no overall effect on the risk of having a baby with birthweight less than 2,500 g (RR, 0.84; 95% CI, 0.68 to 1.03).<br><br>There was no overall effect on the relative risk of the baby being born small-for-gestational age (RR, 1.10; 95% CI, 0.88 to 1.37).<br><br>There was no overall effect on the relative risk of admission to a neonatal intensive care unit (RR, 1.05; 95% CI, 0.94 to 1.18).<br><br>There was no overall effect on the relative risk of a stillbirth or the baby dying before discharge from hospital (RR, 0.89; 95% CI, 0.73 to 1.09).<br><br>Secondary:<br>Not reported |
| Helland et al.[45] (2008)<br><br>Omega-3 fatty acids in the form of cod liver oil (containing 1,183 mg of DHA and 803 mg of EPA) 10 mL/day from 18 weeks of pregnancy until 3 months after delivery<br><br>vs<br><br>corn oil | DB, RCT<br><br>Healthy pregnant women 19 to 35 years of age | N=143<br><br>7 year follow-up of children born to pregnant women receiving treatment intervention | Primary:<br>Cognitive function using the Kaufman Assessment Battery for Children<br><br>Secondary:<br>Not reported | Primary:<br>There were no significant differences in Kaufman Assessment Battery for Children cognitive scores at seven years of age among children whose mothers received cod liver oil during pregnancy as compared to children whose mothers received corn oil during pregnancy.<br><br>Maternal plasma levels of ALA and DHA at 35 weeks of pregnancy were positively associated with sequential processing scale at age seven.<br><br>There was no significant correlation between fatty acid status at birth and BMI at age seven.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| (containing 4,747 mg of linoleic acid and 92 mg of ALA) 10 mL/day from 18 weeks of pregnancy until 3 months after delivery | | | | |
| Dunstan et al.[46] (2008)<br><br>Fish oil (2.2 g DHA and 1.1 g EPA per day) from 20 weeks' gestation until delivery<br><br>vs<br><br>olive oil from 20 weeks' gestation until delivery | DB, RCT<br><br>Pregnant women | N=98<br><br>2.5 year follow-up of children born to pregnant women receiving treatment intervention | Primary:<br>Effects on infant growth and developmental quotients (Griffiths Mental Development Scales), receptive language (Peabody Picture Vocabulary Test) and behavior (Child Behavior Checklist)<br><br>Secondary:<br>Not reported | Primary:<br>There was no significant difference in growth measurements between the fish oil group and the olive oil group. The mean age for both groups was 30 months; the mean height was 93.8 cm for the fish oil group vs 93.3 cm for the olive oil group (P=0.642); the mean weight was 14.5 vs 14.1 kg, respectively (P=0.456); and the head circumference was 49.4 vs 49.8 cm, respectively (P=0.304).<br><br>Children from the fish oil group attained a significantly higher score for eye and hand coordination (P=0.021).<br><br>There was no significant difference mean standard score obtained in the Peabody Picture Vocabulary Test between the fish oil group and the olive oil group (P=0.110).<br><br>Results from the Child Behavior Checklist indicated no significant differences between the mean T scores of the fish oil and olive oil groups for internalizing (P=0.576), externalizing (P=0.706), total problem behavior scales (P=0.548), mean length of phrases (P=0.300) and vocabulary centile score (P=0.650).<br><br>Secondary:<br>Not reported |
| Makrides et al.[47] (2006)<br><br>Marine oil supplement (DHA and EPA dose | MA (6 RCTs)<br><br>Pregnant women | N=2,783<br><br>Variable follow-up | Primary:<br>Risk of pre-eclampsia, preterm birth, and birth weight | Primary:<br>There were no differences in the risk of high blood pressure (RR, 1.09; 95% CI, 0.90 to 1.33) or the incidence of pre-eclampsia (RR, 0.86; 95% CI, 0.59 to 1.27) between marine oil-treated and control groups.<br><br>Women allocated to a marine oil supplement had a mean gestation that |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| ranged from 133 mg to 3 g per day)<br><br>vs<br><br>placebo or no treatment | | | Secondary:<br>Not reported | was 2.6 days longer than women allocated to placebo or no treatment (difference, 2.55 days; 95% CI, 1.03 to 4.07 days). This was not reflected in a clear difference between the two groups in the relative risk of birth before 37 completed weeks (RR, 0.92; 95% CI, 0.79 to 1.07).<br><br>Women allocated to marine oil had a lower risk of giving birth before 34 completed weeks' gestation compared with placebo (RR, 0.69; 95% CI, 0.49 to 0.99).<br><br>Birthweight and birth length were slightly greater in infants born to women in the marine oil group compared with control. However, there was no overall difference between the groups in the relative risk for low birthweight or small-for-gestational babies.<br><br>Secondary:<br>Not reported |
| Makrides et al.[48] (2010)<br><br>DHA supplementation (800 mg of DHA and 100 mg of EPA)<br><br>vs<br><br>vegetable oil capsules without DHA | DB, MC, RCT<br><br>Pregnant women with singleton pregnancies less than 21 weeks gestation | N=2,399 (women)<br><br>N=726 (children)<br><br>6 months post-partum | Primary:<br>High level of maternal depressive symptoms as documented by a score >12 on the Edinburgh Postnatal Depression Scale at six weeks or six months postpartum, neurodevelopment at 18 months of age<br><br>Secondary:<br>Percentage of women medically diagnosed with | Primary:<br>No significant differences were observed between groups in the percentage of women with high levels of depressive symptoms through six months postpartum (RR, 0.85; 95% CI, 0.70 to 1.02).<br><br>No significant differences were observed between groups in mean cognitive composite scores or mean language composite scores (adjusted mean difference, 0.01; 95% CI, -1.36 to 1.37 and adjusted mean difference, -1.42; 95% CI, -3.07 to 0.22 respectively).<br><br>Secondary:<br>No difference was observed between groups in the percentage of women medically diagnosed with depression or receiving treatment for depression during the trial. |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | depression or receiving treatment for depression during pregnancy, at six weeks and six months postpartum | |
| Lewin et al.[49] (2005)<br><br>Omega-3 fatty acid supplementation<br><br>vs<br><br>placebo or no treatment | MA<br><br>Pregnant women, breastfeeding mothers, preterm and term infants | 89 RCT<br><br>Variable duration | Primary:<br>Safety issues, pregnancy outcomes, growth pattern outcomes, neurological development outcomes, visual function outcomes, cognitive development outcomes<br><br>Secondary:<br>Not reported | Primary:<br>*Safety*<br>Omega-3 fatty acids supplementation in pregnant women, breastfeeding mothers, and preterm and term infants, was very well tolerated and did not generate any serious adverse events across the included RCTs.<br><br>*Pregnancy Outcomes*<br>There was no significant difference between intervention groups in the duration of gestation measured as mean of gestational age at delivery.<br><br>Omega-3 fatty acids did not have a significant effect on the proportion of premature deliveries.<br><br>There is inconsistent evidence of the use of omega-3 fatty acids supplements during the second or third trimester of pregnancy to reduce the incidence of premature pregnancies in high- and low-risk populations. The overall effect does not show a significant difference between study arms.<br><br>Supplementation with omega-3 fatty acids did not have a significant effect on the incidence of preeclampsia.<br><br>There was no significant difference in the incidence of gestational hypertension between treatment groups (OR, 1.07; 95% CI, 0.75 to 1.51).<br><br>The mean birth weight was not influenced by the intervention.<br><br>*Growth Pattern Outcomes*<br>There was no statistical difference between infants from mothers that were taking the supplementation with omega-3 and omega-6, or omega-6 fatty |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | acids predominantly, on the weight, length, and head circumference from birth to 12 months of age.<br><br>There was no effect of breast milk, with maternal intake of omega-3 (DHA) or omega-6 fatty acids, on the growth patterns at any time point.<br><br>*Neurological Development Outcomes*<br>One study failed to find a significant difference between groups in maturity as evaluated from the EEGs, neither at day one of life nor at three months of age.<br><br>Two studies showed that maternal breast milk may not have an influence on the neurological outcome, measured with the Psychomotor Development Index scale of the Bayley's Index.<br><br>*Visual Function Outcomes*<br>One study failed to find a significant effect of DHA supplementation during pregnancy on the retinal sensitivity measured at birth in term infants. One cross-sectional study failed to find a statistically significant difference in mean visual function values between the exclusively breastfed group and the infants who were also receiving formula.<br><br>Five studies found that the correlation between the DHA content in breast milk and visual function was not consistent with the clinical outcomes measured in breastfed term infants of mothers who were or were not taking supplements containing high DHA.<br><br>*Cognitive Development Outcomes*<br>There were no differences between groups in the novelty preference (Fagan Test of Infant Intelligence) at six and nine months of age.<br><br>Two studies of breastfed children failed to find a difference in the mean Bayley's Mental Developmental Index score between groups at one or two years of age.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Harper et al.[50] (2010)<br><br>Omega-3 fatty acid supplementation (800 mg of DHA and 1,200 mg of EPA)<br><br>vs<br><br>placebo | DB, MC, RCT<br><br>Pregnant women between 16 and 22 weeks gestation with a history of previous singleton preterm birth | N=852<br><br>14 to 20 weeks | Primary:<br>Delivery before 37 weeks gestation<br><br>Secondary:<br>Delivery before 35 weeks, delivery before 32 weeks, spontaneous preterm delivery, medically indicated preterm delivery, delivery after 40 weeks | Primary:<br>No significant difference was observed between groups in the risk of delivery before 37 weeks (RR, 0.91; 95% CI, 0.77 to 1.07).<br><br>Secondary:<br>No significant differences were observed between groups for any secondary outcome measure. |
| Szajewska et al.[51] (2006)<br><br>Omega-3 fatty acid supplementation | MA (6 RCTs)<br><br>Pregnant women | N=1,278<br><br>Variable duration | Primary:<br>Pregnancy and related maternal and child outcomes<br><br>Secondary:<br>Not reported | Primary:<br>Omega-3 supplementation was associated with a significantly greater duration of pregnancy (difference, 1.57 days; 95% CI, 0.35 to 2.78).<br><br>There was no significant difference between supplemented and non-supplemented subjects in the percentage of preterm deliveries (RR, 0.67; 95% CI, 0.41 to 1.10) or in the rate of low birth weight (RR, 0.66; 95% CI, 0.34 to 0.26).<br><br>There was no significant difference between supplemented and non-supplemented subjects in the rate of preeclampsia or eclampsia (RR, 0.73; 95% CI, 0.22 to 2.37) or in the rate of cesarean delivery (RR, 1.17; 95% CI, 0.79 to 1.74).<br><br>There was no significant difference between supplemented and non-supplemented subjects in the rate of gestational diabetes (RR, 0.73; 95% CI, 0.22 to 2.37).<br><br>There was no significant difference between supplemented and non-supplemented subjects in the placental weight (difference, 10.9 g; 95% CI, 10.4 to 32.2).<br><br>There was no significant difference in birth weight between supplemented |

| Study and Drug Regimen | Study Design and Demographics | Study Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | and non-supplemented control subjects (difference, 54 g; 95% CI, -3.1 to 111).<br><br>There was no significant difference between supplemented and non-supplemented subjects in the length at birth (difference, 0.23 cm; 95% CI, -0.04 to 0.5).<br><br>Supplementation was associated with significantly greater head circumference of the infants in the supplemented group, as compared with those of the non-supplemented control group (difference, 0.26 cm; 95% CI, 0.02 to 0.49).<br><br>Secondary:<br>Not reported |

Study design abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: ALA=α-linolenic acid, BMI=body mass index, CI=confidence interval, DHA=docosahexaenoic acid, EEG=electroencephalogram, EPA=eicosapentaenoic acid, NTD=neural tube defect, OR=odds ratio, RR=relative risk

**Additional Evidence**

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

## IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

| Relative Cost Index Scale | |
|---|---|
| $ | $0-$30 per Rx |
| $$ | $31-$50 per Rx |
| $$$ | $51-$100 per Rx |
| $$$$ | $101-$200 per Rx |
| $$$$$ | Over $200 per Rx |

Rx=prescription

**Table 8. Relative Cost of the Prenatal Vitamins**

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| Iron, folic acid, multivitamins with minerals | Tablet | OB Complete®* | $$ | $ |
| Prenatal vitamins | Capsule | Vinate IC®† | $ | N/A |
| Prenatal vitamins, iron, folic acid | Capsule, chewable tablet, tablet | Concept OB®*, Maxinate®†, Natafort®, Natalvit®†, Nestabs®, OB-Complete Premier®, Prefera OB®, Prenata®, Select-OB®, Tricare®, Vinate II®, Vinate AZ®†, Vinate Care®*, Vinate One®*, Vitafol-OB®, Vitafol-PN®, VP-Era OB Plus®† | $-$$$ | $ |
| Prenatal vitamins, iron, omega-3 fatty acids | Combination package | Bal-Care DHA Essential®† | $$ | N/A |
| Prenatal vitamins, iron, folic acid, DHA | Capsule, combination package | Gesticare DHA®, Natelle One®, Nestabs DHA®, OB Complete®, Paire OB Plus DHA®, Prefera-OB One®, Reaphirm®*, Select-OB+DHA®, Vitafol-OB+DHA®, Vitafol-One®*, Vitafol-Plus® | $-$$$$ | $ |
| Prenatal vitamins, iron, folic acid, | Tablet | Citranatal RX®*, Vinacal®*, | $ | $ |

| Generic Name(s) | Formulation(s) | Example Brand Name(s) | Brand Cost | Generic Cost |
|---|---|---|---|---|
| docusate | | Vinate Calcium®, Vinate GT®*, Vinate PN Care®, Vinate Ultra®*† | | |
| Prenatal vitamins, iron, folic acid, L-methylfolate† | Tablet | N/A | N/A | $ |
| Prenatal vitamins, iron, folic acid, omega-3 fatty acids | Capsule, combination package | Concept DHA®*, Duet DHA Complete®*, Duet DHA Balanced®*, OB Complete With DHA®, OB-Natal One®*†, PR Natal 400®*, PR Natal 430®*, PR Natal 400 EC®, PR Natal 430 EC®, Viva DHA®*† | $-$$ | $ |
| Prenatal vitamins, iron, folic acid, selenium | Tablet | Vinate-M®* | $ | $ |
| Prenatal vitamins, iron, folic acid, vitamin B6 | Tablet | Citranatal B-Calm®* | $ | $ |
| Prenatal vitamins, iron, folic acid, DHA, docusate | Capsule, combination package | Citranatal 90 DHA®, Citranatal Assure®, Citranatal DHA®*, Citranatal Harmony®*, Nexa Select®*, Prenexa®* | $-$$ | $ |
| Prenatal vitamins, iron, folic acid, DHA, fish oil | Capsule | OB Complete 400®, OB Complete One® | $$$ | N/A |
| Prenatal vitamins, iron, folic acid, DHA, L-methylfolate† | Capsule | N/A | N/A | $ |
| Prenatal vitamins, iron, folic acid, DHA, omega-3 fatty acids | Combination package | Prefera-OB Plus DHA® | $ | N/A |
| Prenatal vitamins, iron, folic acid, DHA, ubidecarenone† | Tablet | N/A | N/A | $ |
| Prenatal vitamins, iron, folic acid, DHA, docusate, ubidecarenone | Tablet | Preque 10® | $ | N/A |
| Prenatal vitamins, iron, folic acid, DHA, EPA, fish oil | Capsule | Elite-OB 400®* | $$$ | $$$ |
| Prenatal vitamins, iron, folic acid, DHA, docusate, EPA, fish oil | Capsule | Tricare Prenatal DHA One® | $$$ | $$$ |

*Generic is available in at least one dosage form or strength.
‡ Product is available over-the-counter.
†Fatty acid combination=ALA, DHA, EPA
ALA=Alpha-linolenic acid
DHA=Docosahexaenoic acid
EPA=Eicosapentaenoic acid
N/A=Not available

## X. Conclusions

Women of reproductive age should maintain good nutritional status prior to, during and after pregnancy to minimize health risks to both the mother and child.[1-3] This includes maintaining a healthy weight, participating in physical activity, consuming a variety of foods to meet the Dietary Reference Intake recommendations, as well as appropriate and timely supplementation with multivitamins.[1-3]

It is recommended that that all women planning pregnancy take a supplement containing 400 to 800 µg of folic acid on a daily basis to reduce the risk of neural tube defects.[1,7-11] Women should receive at least 27 mg of elemental iron per day during pregnancy; however, higher amounts are necessary for pregnant women with iron deficiency anemia.[1-3,5,12] There is evidence that maternal consumption of folic acid-containing multivitamins may reduce the risk of neural tube defects, cardiac defects, urinary tract defects, limb defects, as well as other birth defects.[2,13,43] The American Dietetic Association recommends supplementation with a multivitamin for pregnant

women with iron deficiency anemia, poor-quality diets, those who consume no or small amounts of animal source foods, women carrying two or more fetuses, those who smoke or abuse alcohol or drugs, and for women who are infected with human immunodeficiency virus.[1] In addition to a well-balanced diet, supplementation with a folic acid-containing multivitamin should be encouraged in all women of reproductive age to help support healthy pregnancy outcomes.[2]

There are many different prenatal vitamins currently available. The majority of the products contain folic acid and iron, as well as various combinations of vitamins and minerals. Additional nutrients which have been added to some of the prenatal vitamins include aspartame, docusate, L-methylfolate, omega-3 fatty acids and omega-6 fatty acids. Many of the prenatal vitamins are available in a generic formulation, including products which contain omega-3 fatty acids.

There were no clinical trials found in the medical literature that directly compared the various prenatal vitamin preparations. Supplementation with folic acid is clearly beneficial during pregnancy, and adequate intake of iron is necessary to reduce the risk of iron deficiency anemia. There has been recent interest in the health benefits associated with the use of supplemental omega-3 fatty acids during pregnancy. Omega-3 fatty acids are necessary for nervous tissue growth and function, and dietary intake has a variety of health benefits.[14] Some studies have suggested that omega-3 fatty acids may improve fetal/neonatal visual and neural growth and help prevent low birth weight when taken as a supplement during pregnancy.[2-3,15] Several meta-analyses have evaluated the use of supplemental omega-3 fatty acids during pregnancy. In general, the results of these analyses have not found a significant difference in pregnancy-related outcomes.[45-47,49-51] This includes assessment of maternal outcomes (blood pressure, preeclampsia and preterm delivery) and child outcomes (neurological development, growth patterns, visual function and cognitive development).[45-47,49,51] There is insufficient evidence regarding the supplemental use of omega-3 fatty acids and the effects on pregnancy-related maternal and child outcomes.

There is insufficient evidence to support that one brand prenatal vitamin is safer or more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

## XI. Recommendations

No brand prenatal vitamin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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