Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
August 11, 2010

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Pharmacotherapy Review of Genitourinary Smooth Muscle Relaxants
AHFS Class 861200
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I. Overview

Urinary incontinence (UI) is the involuntary leakage of urine, which may be classified as urge, stress, overflow or mixed incontinence.[15] Urge incontinence is accompanied by a sense of urgency, while stress incontinence generally occurs with effort, exertion, sneezing or coughing. Overflow incontinence is associated with dribbling and/or continuous leakage due to incomplete bladder emptying. Overactive bladder (OAB) is a functional disorder characterized by urinary urgency, daytime frequency (>8 voids during the daytime), nocturia (>1 void at night), with or without incontinence.[17,82] UI and OAB may be due to lower urinary tract dysfunction or secondary to non-genitourinary disorders. The most common cause of OAB is overactivity of the bladder's detrusor muscle. Symptoms may be assessed by patient history, the use of validated questionnaires, and/or bladder diaries. Clinical testing (e.g., bladder stress test, postvoid residual volume testing, urine flow rate and urodynamic testing) may help identify the pathology, but are not always necessary for diagnosis or initiation of therapy.[15,17] UI and OAB cause both physical and psychological morbidity, as well as adversely impact quality of life.[15] Initial treatment options include lifestyle modifications (weight loss and dietary changes), behavioral therapy (bladder training, physical therapy and toileting assistance) and pharmacologic therapy.[16-17] Neurogenic lower urinary tract disorder (NLUTD) is caused by a lesion at any level of the nervous system (e.g., cerebral cortex, spinal cord or peripheral nervous system).[18-19] The lesion interferes with the normal nerve pathways associated with urination. Early diagnosis and treatment of NLUTD is essential for both congenital and acquired disorders as irreversible changes may occur.[19]

Normal voiding is dependent on acetylcholine-induced stimulation of muscarinic receptors on bladder smooth muscle. There are 5 muscarinic receptor subtypes, of which M1, M2 and M3 mediate bladder contractility. Muscarinic receptors are also found in the gastrointestinal tract, salivary glands and tear ducts. Anticholinergic drugs with antimuscarinic effects increase bladder capacity, decrease urgency and are useful for the treatment of urge incontinence.[16] Darifenacin, fesoterodine, solifenacin, tolterodine and trospium are muscarinic receptor antagonists.[4-6,11-14] Flavoxate is an antispasmodic which exerts its effects directly on muscle and counteracts the smooth muscle spasm of the urinary tract.[1] Oxybutynin has a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle.[7-10] Some antimuscarinic agents claim to have greater affinity for specific receptor subtypes that mediate bladder contractility, but the clinical significance of this is unclear. The most common adverse effects associated with the use of antimuscarinic agents include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. These agents may also cause confusion or cognitive impairment in the elderly.[16]

The genitourinary smooth muscle relaxants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Flavoxate, oxybutynin immediate-release syrup and tablet, as well as oxybutynin extended-release tablets are available in a generic formulation.

Table 1. Genitourinary Smooth Muscle Relaxants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Darifenacin	extended-release tablet	Enablex®	not applicable
Fesoterodine	extended-release tablet	Toviaz®	not applicable
Flavoxate	tablet	N/A	not applicable
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	not applicable
Solifenacin	tablet	Vesicare®	not applicable
Tolterodine	extended-release capsule, tablet	Detrol®, Detrol LA®	not applicable
Trospium	extended-release capsule, tablet	Sanctura®, Sanctura XR®	not applicable

*Generic is available in at least one dosage form or strength.
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 genitourinary smooth muscle relaxants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Genitourinary Smooth Muscle Relaxants

Clinical Guideline	Recommendation(s)

Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: **Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse, and Fecal Incontinence**[81] **(2010)**	<u>Initial Management of Urinary Incontinence in Men</u>
	• For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Lifestyle interventions
	  o Supervised pelvic floor muscle training for men with post-radical prostatectomy SUI
	  o Scheduled voiding regimes for OAB
	  o Antimuscarinic drugs for OAB symptoms with or without urgency incontinence and the patient has no evidence of significant post-void residual urine
	  o Alpha adrenergic antagonists (α-blockers) can be added if it is thought that there may also be bladder outlet obstruction
	<u>Initial Management of Urinary Incontinence in Women</u>
	• For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Advice on caffeine reduction and weight reduction
	  o Supervised pelvic floor muscle training and vaginal cones for women with stress incontinence
	  o Supervised bladder training for OAB
	  o If estrogen deficiency and/or UTI is found, the patient should be treated at initial assessment and then reassessed after a suitable interval
	  o Antimuscarinics for OAB symptoms with or without urgency incontinence
	  o Duloxetine may be considered for stress urinary incontinence
	<u>Initial Management of Neurogenic Urinary Incontinence</u>
	• Conservative treatment modalities (often in combination):
	  o Intermittent catheterization
	  o Behavioral treatment
	  o Timed voiding
	  o External Appliances
	  o Antimuscarinics
	  o Alpha-blockers
	  o Intravesical ES
	  o Bladder expression
	  o Triggered voiding
	  o Indwelling catheter
	<u>Management of Urinary Incontinence in Frail Older Persons</u>
	• Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis.
	• In some frail elders the only possible outcome may be contained UI (managed with pads), especially for persons with minimal mobility (require assistance of >2 persons to transfer), advanced dementia (unable to state their name), and/or nocturnal UI.
	• Conservative and behavioral therapy for UI include lifestyle changes, bladder training for more fit alert patients, and prompted voiding for frailer, more impaired patients.
	• For select cognitively intact patients, pelvic muscle exercises may be considered. Antimuscarinics may be added to conservative therapy of

Clinical Guideline	Recommendation(s)
	urgency UI. • Alpha-blockers may be cautiously considered in frail men with suspected prostatic outlet obstruction. • DDAVP (vasopressin) has a high risk of severe hyponatremia in frail persons and should not be used.

European Association of Urology (EAU): **Guidelines on Urinary Incontinence[83] (2010)**	<u>Treatment of overactive bladder (OAB)/detrusor overactivity (DO)</u>
	• Drugs may be efficacious in some patients with urinary incontinence; however, adverse events lead to discontinuation after short periods of time. They are best used as an adjuvant to conservative and surgical therapy.
	• Meta-analyses of antimuscarinic drugs have shown they provide a significant clinical benefit. More research is needed to decide the best drugs for first-, second-, or third-line treatment. None of the commonly used antimuscarinic drugs (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium) is an ideal first-line treatment for all OAB/DO patients.
	• Optimal treatment should be individualized, considering the patient's co-morbidities, concomitant medications and the pharmacological profiles of the different drugs.
	<u>Hormonal treatment of Urinary Incontinence (UI)</u>
	• Estrogens (alone or with a progestogen) have achieved poor results in UI and should not be used as there is no evidence to show they have a direct effect on the lower urinary tract.
	• Estrogens may be effective in alleviating OAB symptoms and local administration may be the most beneficial route of administration.
	<u>Desmopressin</u>
	• Desmopressin was well tolerated and resulted in a significant improvement in UI compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. Quality of life also improved.
	<u>Incontinence in Men</u>
	• For men with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Lifestyle interventions
	  o Pelvic floor muscle training ± biofeedback
	  o Scheduled voiding (bladder training)
	  o Antimuscarinics (overactive bladder ± urgency incontinence) and alpha adrenergic antagonists (if also bladder outlet obstruction)
	<u>Incontinence in Women</u>
	• For women with stress, urgency or mixed urgency/stress incontinence, initial treatment should include:
	  o Lifestyle interventions
	  o Pelvic floor muscle training for stress urinary incontinence (SUI) or overactive bladder (OAB)
	  o Bladder retraining for OAB
	  o Duloxetine (SUI) or antimuscarinics (OAB + urgency incontinence)
	<u>Management of Urinary Incontinence in Frail Older Persons</u>
	• Initial treatment should be individualized and influenced by goals of care, treatment preferences, and estimated remaining life expectancy, as well as the most likely clinical diagnosis.
	• In some frail elders the only possible outcome may be contained UI (managed with pads), especially for persons with minimal mobility (require assistance of >2 persons to transfer), advanced dementia

Clinical Guideline	Recommendation(s)
	(unable to state their name), and/or nocturnal UI. • Conservative and behavioral therapy for UI include lifestyle changes, bladder training for more fit alert patients, and prompted voiding for frailer, more impaired patients. • For select cognitively intact patients, pelvic muscle exercises may be considered. Antimuscarinics may be added to conservative therapy of urgency UI. • A trial of antimuscarinic drugs may be considered as an adjunct to conservative therapy of urgency UI. • Alpha-blockers may be cautiously considered in frail men with suspected outlet obstruction from prostate disease. • DDAVP carries a high risk of clinically significant hyponatremia and should not be used in frail/older persons to treat nocturia or nocturnal polyuria.
Neurogenic Bladder Society (NBS): **Clinical Guidelines for Overactive Bladder[17] (2009)**	<u>Behavioral Therapy</u> • Behavioral therapy can include lifestyle guidance, bladder training, physical therapy and toileting assistance. • Behavioral therapy is minimally invasive with no adverse reactions and combination therapy with other forms of treatment is also possible. • Behavioral therapy should be considered as the first-line choice for initial treatment of OAB. • The efficacy of combined behavioral therapy and drug therapy over monotherapy has yet to be determined, but it is the recommended treatment approach. <u>Drug Therapy</u> • Drug therapy forms the basis of treatment for overactive bladder (OAB). • The drugs for which efficacy and safety have been investigated are the anticholinergic agents. These are most commonly used for the treatment of OAB. • When using anticholinergic drugs, it is necessary to consider adverse reactions due to blockade of the systemic muscarine receptors. <u>Anticholinergic Drugs</u> • Oxybutynin has a direct relaxing effect and paralyzing effect on smooth muscle in addition to its antimuscarinic activity. It has been extensively evaluated and its efficacy has been well demonstrated. The incidence of adverse reactions associated with its antimuscarinic activity is higher than that of other anticholinergic drugs. It is recommended that treatment is started from a low dose and titrated gradually to determine the optimal dose. Oxybutynin can pass through the blood-brain barrier potentially causing central nervous system adverse events (cognitive impairment, etc.). Caution is required in elderly patients. • Tolterodine has no selectivity for muscarinic receptor subtypes, is well distributed to and has a high binding affinity for the bladder, and as compared with the salivary glands, is highly selective for the bladder. It has been extensively evaluated and there is substantial evidence for efficacy and safety in OAB patients, including the elderly and patients with severe OAB. • Solifenacin is highly selective for the muscarinic receptor M3, and is more highly selective for the bladder than for the salivary glands. It has been shown to be effective for urgency, frequency, and urge urinary incontinence in OAB. • Flavoxate has no antimuscarinic activity, but appears to have a moderate calcium antagonistic action, inhibitory effect on

Clinical Guideline	Recommendation(s)

	phosphodiesterase, and a local relaxant effect on smooth muscle. Flavoxate has been observed to have almost no adverse reactions, but its efficacy has not been adequately evaluated.
	• Darifenacin is high selectivity for the M3 receptor subtype, and it has shown a higher selectivity for the bladder than the salivary glands in animal studies. Concern has been raised about adverse reactions involving the salivary glands and gastrointestinal tract, in which M3 receptors are numerous.
	<u>Antidepressants</u>
	• Several types of tricyclic antidepressants are indicated for enuresis or nocturnal enuresis, with imipramine being the most commonly used drug. Imipramine appears to be useful for nocturnal enuresis in children, but its usefulness as a therapeutic agent for OAB is yet to be adequately evaluated.
	<u>Botulinum Toxin</u>
	• Botulinum toxin is believed to inhibit bladder contraction by blocking the release of acetylcholine from cholinergic nerves, primarily by causing chemical denervation.
	• Injection of botulinum toxin into the bladder wall is believed to be a promising therapeutic method for OAB, but its usefulness is yet to be adequately explored.
	<u>Efficacy of Drug Therapy for OAB Symptoms in BPH Patients</u>
	• α_1-blockers are first-line drug therapy for OAB symptoms in BPH patients, but their long-term efficacy in patients without lower urinary tract obstruction has yet to be proven.
	• Randomized controlled studies to demonstrate the efficacy and safety of anticholinergic drugs for OAB symptoms associated with BPH have yet to be performed.
	• Despite the fact that anticholinergic drugs may be effective in some BPH patients with OAB symptoms, there is ample risk of causing acute urinary retention or chronic urinary retention.
	• The therapeutic positioning of anticholinergic drugs for men with lower urinary tract symptoms is uncertain, and they are contraindicated in patients with severe lower urinary tract obstruction or urinary retention.
	• It remains uncertain whether combination therapy with an α_1-blocker and an anticholinergic drug is superior to α_1-blocker monotherapy in BPH patients with OAB symptoms.
	<u>Practical Guidelines for Drug Therapy for Overactive Bladder: Rules for Treatment with Anticholinergic Drugs, Classified by Sex and Age</u>
	• OAB in Women:
	  ○ Anticholinergic drugs can be administered immediately.
	  ○ If voiding symptoms, as well as OAB symptoms, are present, anticholinergic drugs should be administered with caution.
	  ○ Since OAB and impaired detrusor contractility may both be present in elderly women (80 years or older) in particular, patients should be referred to a urological specialist if voiding symptoms are severe or if residual urine is copious (50 mL or more).
	• OAB in men under 50 years of age:
	  ○ For OAB in relatively young men, it is recommended that patients be evaluated by a urological specialist at least once, as there may be an underlying comorbid neurological disease or urological disease.
	• OAB in men aged 50 years or older:

Clinical Guideline	Recommendation(s)
	○ Because there is a high probability of OAB as a complication of benign prostatic hyperplasia, give top priority to starting an α_1-blocker if voiding symptoms are confirmed. ○ If there is no improvement in OAB symptoms, an anticholinergic drug can be coadministered. However, since there is not adequate evidence regarding this combination, the patient should also be referred to a urological specialist.
National Institute for Health and Clinical Excellence (NICE): **Urinary Incontinence: The Management of Urinary Incontinence in Women**[20] **(2006)**	Behavioral Therapy • Bladder training should be offered as first-line treatment to women with urge or mixed urinary incontinence (UI). • If women do not achieve satisfactory benefit from bladder training, the combination of an antimuscarinic agent and bladder training should be considered if frequency is a troublesome symptom. • In women with UI who also have cognitive impairment, prompted and timed voiding toileting programs are recommended as strategies for reducing leakage episodes. Pharmacologic Therapy • Immediate-release oxybutynin should be offered to women with OAB or mixed UI as first-line drug treatment if bladder training has been ineffective. • If immediate-release oxybutynin is not well tolerated, darifenacin, solifenacin, tolterodine, trospium, or an extended-release or transdermal formulation of oxybutynin should be considered as alternatives. • Propiverine should be considered as an option to treat frequency of urination in women with OAB, but is not recommended for the treatment of UI. • Flavoxate, propantheline and imipramine should not be used for the treatment of UI or OAB in women. • The use of desmopressin may be considered to reduce nocturia in women with UI or OAB who find it a troublesome symptom. • Duloxetine is not recommended as a first-line treatment for women with predominant stress UI. Duloxetine should not routinely be used as a second-line treatment for women with stress UI, although it may be offered as second-line therapy if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment. • Systemic hormone replacement therapy is not recommended for the treatment of UI. • Intravaginal estrogens are recommended for the treatment of OAB symptoms in postmenopausal women with vaginal atrophy. Complementary Therapy • Complementary therapies are not recommended for the treatment of UI or OAB.
American College of Obstetricians and Gynecologists (ACOG): **Urinary Incontinence in Women**[21] **(2005)**	• Behavioral therapy (e.g., bladder training and prompted voiding) improves symptoms of urge and mixed incontinence and can be recommended as a noninvasive treatment in many women. • Pelvic floor training appears to be an effective treatment for adult women with stress and mixed incontinence and can be recommended as a noninvasive treatment for many women. • Pharmacologic agents may have a small beneficial effect on improving symptoms of detrusor overactivity in women. • The anticholinergic drugs, oxybutynin and tolterodine, have been shown to have a small beneficial effect as therapy for urge incontinence. However, for many of the outcomes studied, the observed differences between treatment with anticholinergic

Clinical Guideline	Recommendation(s)
	medications and placebo may be of questionable clinical significance. No significant difference among these agents was reported. • The most typical side effect of anticholinergic therapy is dry mouth. Other side effects most frequently reported include blurred vision, constipation, nausea, dizziness, and headache. • Alternative drugs, new drugs, and new formulations of existing drugs are all available, but limited data exist on which to base recommendations. • Oral estrogen regimens cannot be recommended as treatment or prevention for any type of urinary incontinence.
Scottish Intercollegiate Guidelines Network (SIGN): **Management of Urinary Incontinence in Primary Care: A National Clinical Guideline[22] (2004)**	<u>Behavioral Therapy</u> • Pelvic floor muscle exercises should be the first choice of treatment offered to patients suffering from stress or mixed incontinence. • Pelvic floor muscle exercises should be considered as part of a treatment plan for patients with urge urinary incontinence. • Pelvic floor muscle exercise treatment should be considered for patients following radical prostate surgery. • Bladder retraining should be offered to patients with urge urinary incontinence. <u>Pharmacologic Therapy of Stress Incontinence</u> • Published studies have reported conflicting evidence for the efficacy of estrogens in treating stress incontinence. • Imipramine has been used clinically to treat stress incontinence, but there are no studies available to support its use. • Duloxetine should be used only as part of an overall management strategy in addition to pelvic floor muscle exercises. A 4-week trial of is recommended for female patients with moderate-to-severe stress incontinence. Patients should be reviewed again after 12 weeks of therapy to assess progress and determine whether it is appropriate to continue treatment. <u>Pharmacologic Therapy of Detrusor Overactivity and Urge Incontinence</u> • Oxybutynin, tolterodine, trospium and propiverine are effective in reducing detrusor overactivity (urgency and urge incontinence). Comparative studies of the effectiveness of detrusor selective antimuscarinics have shown all the drugs to be equally effective. • The most common side effects of antimuscarinic drugs are dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. • Oxybutynin immediate-release preparation has the highest incidence of side effects. • Several studies have shown sustained-release antimuscarinic preparations are associated with a lower incidence and severity of side effects than immediate-release preparations. • A trial of oxybutynin, propiverine, tolterodine, or trospium should be given to patients with significant urgency with or without urge incontinence. • Antimuscarinic therapy should be tried for a period of 6 weeks to enable an assessment of the benefits and side effects. Treatment should be reviewed after 6 months to assess continued need. • Studies of the efficacy of flavoxate have shown mixed results; few adverse events were reported. • There is inadequate evidence to support the use of imipramine for the treatment of detrusor overactivity. • There is no evidence to date for combining therapy in a patient with mixed urge and stress incontinence.

Clinical Guideline	Recommendation(s)
European Association of Urology (EAU) and European Society for Paediatric Urology (ESPU): **Guidelines on Pediatric Urology: Management of Neurogenic Bladder in Children[18] (2009)**	Early Management With Clean Intermittent Catheterization • Management of neurogenic bladder in infants has demonstrated that children do not have upper tract deterioration when managed early with clean intermittent catheterization and anticholinergic medication. • Clean intermittent catheterization should be started soon after birth in all babies, especially in those with signs of possible outlet obstruction. Medical Therapy • Oxybutynin, tolterodine, trospium and propiverine are the most frequently used drugs for the treatment of neurogenic bladder. Most of the studies have been conducted with oxybutynin. • The use of medication to facilitate emptying in children with neurogenic bladder has not been well studied. • The use of α-adrenergic blockade in children with neurogenic bladder has resulted in a good response rate, but the studies lacked controls and long-term followup is warranted. Botulinum Toxin Injections • Injection of botulinum toxin into the detrusor is an alternative treatment option for neurogenic bladders, which are refractory to anticholinergics and remain in a small-capacity, high-pressure state. • There is a lack of prospective controlled studies of botulinum toxin in children. Injection of botulinum toxin in therapy-resistant bladders appears to be an effective and safe treatment alternative. Treatment appears to be more effective on bladders with a more active component. Stiff bladders without an active component are unlikely to respond to botulinum toxin. It is unclear how many times this treatment can be repeated.
European Association of Urology (EAU): **Guidelines on Neurogenic Lower Urinary Tract Dysfunction (NLUTD)[19] (2008)**	Treatment Goals • The primary goals for the treatment of NLUTD are: protection of the upper urinary tract, improvement of urinary continence, improvement of the patient's quality of life, and restoration of (parts of) the normal lower urinary tract function. Assisted Bladder Emptying • Incomplete bladder emptying is a risk factor for urinary tract infections, for developing high intravesical pressure during the filling phase, and for incontinence. • Methods to improve the voiding process should be practiced in patients with NLUTD. Lower Urinary Tract Rehabilitation • Behavioral modification includes prompted voiding, timed voiding (bladder training), and modification of the life pattern improve incontinence. • Pelvic floor muscle exercises improve continence. • Pelvic floor electrostimulation is used to improve the effect of pelvic floor muscle exercises, to teach the patient how to contract the pelvic floor, and to improve patient compliance with the exercises. • Biofeedback can be used for supporting the voiding pattern modification. Drug Treatment • A medical treatment for NLUTD is not available. Most drugs only resolve part of the problem, or are adjunct to other measures. • Detrusor overactivity can be treated by anticholinergic agents. Treatment is generally life-long; however, increased drug tolerance and adverse events are problematic in patients with NLUTD. These patients need a higher dose then other patients with overactive detrusor, which may lead to discontinuation of the therapy because of

Clinical Guideline	Recommendation(s)
	adverse events. • Oxybutynin, trospium, and propiverine are established medical treatments. These agents have different tolerability profiles and an alternative anticholinergic agent may be prescribed if the patient experiences adverse effects with one. • In general, medical therapy does not improve detrusor contractility. • Alpha-blockers have been used successfully on occasion for decreasing bladder outlet resistance. • Several drugs have been shown to be effective for the treatment of mild stress incontinence, but there are few studies in patients with NLUTD. <u>Electrical Neuromodulation</u> • Electrical stimulation of the pudendal nerve afferents produces a strong inhibition of the micturition reflex and of the detrusor contraction. <u>External Appliances</u> • Social continence may be achieved by collecting the urine when incontinence cannot be resolved by any other methods. • Condom catheters with urine collection devices are a practical method for men. Incontinence pads may also offer a reliable solution.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the genitourinary smooth muscle relaxants 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 Genitourinary Smooth Muscle Relaxants[1-14]

Indication	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin	Solifenacin	Tolterodine	Trospium
Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	✔	✔		✔ †§	✔	✔	✔
For symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis, urethrocystitis and urethrotrigonitis			✔				
Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)				✔ ‡			
Treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)				✔ §			

†Transdermal formulations.
‡Immediate-release oral formulation.
§Extended-release oral formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the genitourinary smooth muscle relaxants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Genitourinary Smooth Muscle Relaxants[1-14]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Darifenacin	15-25	98	Liver, extensive; Intestinal wall	Renal (60) Feces (40)	13-19
Fesoterodine	52	50	Liver, extensive	Renal (70) Feces (7)	4-7
Flavoxate	Not reported	Not reported	Not reported	Renal (57)	Not reported
Oxybutynin	IR: 7 ER: 156-187	Not reported	Liver; Intestinal wall	Renal (<0.1)	Gel: 64 ER: 13.2 IR: 2-3 Patch: 6-7
Solifenacin	90	98	Liver	Renal (3-6) Feces (22.5)	40-68
Tolterodine	IR: 77	Not reported	Liver	Renal (77) Feces (17)	IR: 1.9-3.7
Trospium	IR: 9.6	IR: 50-85 ER:48-78	Liver	Renal (5.8) Feces (85.2)	IR: 18.3 ER: 35

ER=extended-release formulation, IR=immediate-release formulation

V. Drug Interactions

Significant drug interactions with the genitourinary smooth muscle relaxants are listed in Table 5.

Table 5. Significant Drug Interactions with the Genitourinary Smooth Muscle Relaxants[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Oxybutynin (transdermal gel)	1	Disulfiram	The combination of transdermal oxybutynin gel and disulfiram may produce acute alcohol intolerance. Hypotension and cardiovascular collapse may also occur. The effects of this interaction are dose-dependent. Inhibition of aldehyde dehydrogenase by disulfiram leads to the development of toxic intermediate metabolites.
Darifenacin, Fesoterodine, Solifenacin, Tolterodine	2	Protease Inhibitors	Inhibition of cytochrome P450 3A4 by protease inhibitors may decrease the metabolic elimination of darifenacin. Plasma concentrations and pharmacologic effects of darifenacin may be increased.
Darifenacin, Fesoterodine, Solifenacin, Tolterodine	2	Imidazoles	Inhibition of cytochrome P450 3A4 by imidazoles may decrease the metabolic elimination of darifenacin. Plasma concentrations and pharmacologic effects of darifenacin may be increased.
Darifenacin, Fesoterodine, Solifenacin, Tolterodine	2	Macrolides	Inhibition of cytochrome P450 3A4 by macrolides may decrease the metabolic elimination of darifenacin. Plasma concentrations and pharmacologic effects of darifenacin may be increased.

Generic Name(s)	Significance Level	Interaction	Mechanism
Darifenacin, Fesoterodine, Solifenacin, Tolterodine	2	Nefazodone	Inhibition of cytochrome P450 3A4 by nefazodone may decrease the metabolic elimination of darifenacin. Plasma concentrations and pharmacologic effects of darifenacin may be increased.
Darifenacin, Fesoterodine, Flavoxate, Oxybutynin (oral), Solifenacin, Tolterodine, Trospium	2	Potassium Preparations	Anticholinergic agents may slow gastrointestinal motility and cause delay in tablet passage through the gastrointestinal tract.
Oxybutynin, Trospium	2	Phenothiazines	The antipsychotic effectiveness of phenothiazines may be decreased by oxybutynin, which may cause additive anticholinergic toxicity. This may be due to additive central and peripheral anticholinergic effects, as well as decreased phenothiazine bioavailability.
Oxybutynin (transdermal gel)	2	Metronidazole	Metronidazole may inhibit aldehyde dehydrogenase-medicated metabolism of ethanol and cause a toxic accumulation of acetaldehyde. The combination of metronidazole and transdermal oxybutynin gel may produce alcohol intolerance reactions.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the genitourinary smooth muscle relaxants are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Genitourinary Smooth Muscle Relaxants[1-14]

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Cardiovascular								
Angina	-	<1	-	-	-	-	-	-
Arrhythmia	-	-	-	1-5	✔ §	-	-	-
Chest pain	-	<1	-	1-5	-	-	2	<1
Edema	-	-	-	1-5	-	≤1	-	-
Fluid retention	-	-	-	1-5	-	-	-	-
Heart rate increased	-	<1	-	-	-	-	-	-
Hypertension	≥1	-	-	1-5	-	≤1	-	-
Hypertensive crisis	-	-	-	-	-	-	-	<1
Hypotension	-	-	-	1-5	-	-	-	-
Myocarditis	-	-	-	-	✔ §	-	-	-
Palpitations	✔	-	✔	1-5	-	-	✔	<1
Peripheral edema	≥1	1	-	1-5	-	-	✔	-
QT_c prolongation	-	<1	-	1-5	-	<1	-	-
Supraventricular tachycardia	-	-	-	-	-	-	-	<1
Syncope	-	-	-	-	-	-	-	<1
Tachycardia	-	-	✔	1-5	✔ §	-	✔	✔
Torsade de pointes	-	-	-	-	-	<1	-	-
T-wave inversion	-	-	-	-	-	-	-	<1
Central Nervous System								
Agitation	-	-	-	1-5	-	-	-	-
Anxiety	-	-	-	-	-	-	1†	-
Confusion	✔	-	✔	-	-	<1	✔	-
Delirium	-	-	-	-	-	-	-	<1
Depression	-	-	-	1-5	-	-	-	-
Disorientation	-	-	-	-	-	-	✔	-
Dizziness	<2	-	-	4-17	2-3‡	≤1	2†, 5γ	-
Drowsiness	-	-	✔	-	-	-	-	-
Fatigue	-	-	✔	1-5	2‡	1-2	2†, 4γ	2
Hallucinations	✔	-	-	1-5	✔ §	<1	✔	<1
Headache	7	-	✔	6-10	2‡	3-6	7†, 6γ	4-7

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Heat prostration	-	<1	-	-	-	-	-	-
Hyperpyrexia	-	-	✔	-	-	-	-	-
Insomnia	-	1	-	1-6	-	-	-	-
Memory impairment	-	-	-	1-5	-	-	✔	-
Nervousness	-	-	✔	1-7	-	-	-	-
Pain	≥1	-	-	1-7	-	-	-	-
Psychotic disorder	-	-	-	1-5	-	-	-	-
Seizure	-	-	-	1-5	-	-	-	-
Somnolence	-	-	-	2-14	-	-	3	<1
Vertigo	-	-	✔	-	-	-	-	-
Dermatological								
Application site reaction	-	-	-	-	5‡, 17§	-	-	-
Dermatitis	-	-	-	-	5‡	-	-	-
Dry skin	≥1	-	-	1-5	-	-	1	✔
Erythema	-	-	-	-	5‡, 6-8§	-	-	-
Flushing	-	-	-	1-5	-	-	-	-
Irritation	-	-	-	-	5‡	-	-	-
Papules	-	-	-	-	5‡	-	-	-
Pruritus	≥1	-	-	1-5	1-5‡, 14§	<1	-	-
Rash	≥1	1	✔	1-5	3§	<1	-	<1
Stevens-Johnson syndrome	-	-	-	-	-	-	-	<1
Sweating decreased	-	-	-	1-5	✔ §	-	-	-
Urticaria	-	-	✔	-	-	<1	-	-
Vesicles	-	-	-	-	3§	-	-	-
Endocrine and Metabolic								
Hyperglycemia	-	-	-	1-5	-	-	-	-
Gastrointestinal								
Abdominal pain	2-4	1	-	1-5	-	1-2	4†, 5γ	1-3
Abdominal distention	-	-	-	-	-	-	-	<2
Aptyalism	-	-	-	1-5	-	-	-	-
Constipation	15-21	4-6	✔	7-15	1‡, 3§	5-13	6†, 7γ	9-10
Diarrhea	-	-	-	1-9	3§	-	✔	-
Diverticulitis	-	<1	-	-	-	-	-	-
Dysgeusia	-	-	-	1-5	-	-	-	-
Dyspepsia	3-8	2	-	5-7	-	1-4	3†, 4γ	1-2
Dysphagia	-	-	-	1-5	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Eructation	-	-	-	1-5	-	-	-	-
Fecal impaction	-	-	-	-	-	<1	-	-
Feces hard	-	-	-	-	-	-	-	<1
Flatulence	-	-	-	1-5	-	-	-	1-2
Gastritis	-	-	-	-	-	-	-	<1
Gastroenteritis	-	<1	-	-	2‡	-	-	-
Gastrointestinal obstruction	-	-	-	-	-	<1	-	-
GERD	-	-	-	1-5	-	-	-	-
GI motility decreased	-	-	-	1-5	-	-	-	-
Hoarseness	-	-	-	1-5	-	-	-	-
Irritable bowel syndrome	-	<1	-	-	-	-	-	-
Loose stools	-	-	-	1-5	-	-	-	-
Nausea	2-4	1-2	✔	2-12	-	2-3	-	1
Pharyngolaryngeal pain	-	-	-	1-5	-	-	-	-
Taste abnormal	-	-	-	-	-	-	-	✔
Thirst	-	-	-	1-5	-	-	-	-
Tongue coated	-	-	-	1-5	-	-	-	-
Vomiting	≥1	-	✔	1-5	-	-	-	✔
Weight gain	≥1	-	-	-	-	-	1	-
Xerostomia	19-35	19-35	✔	29-71	7-8‡, 4-10§	11-28	23†, 35γ	9-22
Genitourinary								
Cystitis	-	-	-	1-5	-	-	-	-
Dysuria	-	1-2	✔	1-5	2§	-	1†, 2γ	-
Impotence	-	-	-	1-5	✔ §	-	-	-
Pollakiuria	-	-	-	1-5	-	-	-	-
Urinary retention	✔	1	-	6	-	≤1	-	≤1
Urinary tract infection	4-5	3-4	-	-	7‡	3-5	-	1-7
Vaginitis	≥1	-	-	-	-	-	-	-
Hematologic								
Leukopenia	-	-	✔	-	-	-	-	-
Hepatic								
ALT increased	-	1	-	-	-	-	-	-
GGT increased	-	1	-	-	-	-	-	-
Musculoskeletal								
Arthralgia	≥1	-	-	1-5	-	-	2	-
Back pain	≥1	1-2	-	1-5	-	-	-	<1

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Rhabdomyolysis	-	-	-	-	-	-	-	<1
Weakness	<3	-	-	3-7	-	-	-	-
Ocular								
Abnormal vision	≥1	-	-	-	-	-	1†, 2γ	-
Blurred vision	-	<1	✔	1-10	-	4-5	-	1
Cycloplegia	-	-	-	1-5	✔ §	-	-	-
Dry eyes	2	1-4	-	3-6	-	≤2	3	1-2
Eye irritation	-	-	-	1-5	-	-	-	-
Intraocular pressure increased	-	-	✔	-	-	-	-	-
Keratoconjunctivitis sicca	-	-	-	1-5	-	-	-	-
Mydriasis	-	-	-	1-5	-	-	-	-
Vision changes	-	-	-	-	3§	-	-	-
Respiratory								
Asthma	-	-	-	1-5	-	-	-	-
Bronchitis	≥1	-	-	1-5	-	-	2	-
Cough	-	1-2	-	1-5	-	≤1	-	-
Dry throat	-	1-2	✔	1-5	-	-	-	-
Nasal congestion	-	-	-	1-5	-	-	-	-
Nasal dryness	-	-	-	1-5	-	-	-	1
Nasopharyngitis	-	-	-	1-5	3‡	-	-	3
Pharyngitis	≥1	-	-	-	-	-	-	-
Rhinitis	≥1	-	-	2-6	-	-	-	-
Sinus congestion	-	-	-	1-5	-	-	-	-
Sinus headache	-	-	-	1-5	-	-	-	-
Sinusitis	≥1	-	-	1-5	-	-	2†	-
Upper respiratory tract infection	-	2-3	-	1-5	-	-	-	-
Other								
Anaphylactoid reactions	-	-	-	-	-	-	<1	-
Anaphylaxis	-	-	-	-	-	-	-	<1
Angioedema	✔	-	-	-	-	-	<1	-
Angioneurotic edema	-	-	-	-	-	<1	-	<1
Extremity pain	-	-	-	1-5	-	-	-	-
Flank pain	-	-	-	1-5	-	-	-	-
Flu-like syndrome	1-3	-	-	-	-	-	3	-
Fungal infection	-	-	-	1-5	-	-	-	-

Adverse Events	Darifenacin	Fesoterodine	Flavoxate	Oxybutynin (Oral)	Oxybutynin (Transdermal)	Solifenacin	Tolterodine	Trospium
Hypersensitivity	✔	-	-	-	-	<1	-	-
Infection	-	-	-	-	-	-	1	-
Influenza	-	-	-	-	-	≤2	-	2
Lactation suppression	-	-	-	1-5	✔ §	-	-	-

✔ Percent not specified
- Event not reported
‡Transdermal gel formulation.
§Transdermal patch formulation.
†Extended-release formulation.
γ Immediate-release formulation.

VII. Dosing and Administration

The usual dosing regimens for the genitourinary smooth muscle relaxants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Genitourinary Smooth Muscle Relaxants[1-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Darifenacin	Overactive Bladder: 7.5 to 15 mg once daily	The safety and effectiveness have not been established in pediatric patients.	Tablet (ER): 7.5 mg 15 mg
Fesoterodine	Overactive Bladder: 4 to 8 mg once daily	The safety and effectiveness have not been established in pediatric patients.	Tablet (ER): 4 mg 8 mg
Flavoxate	Urinary Tract Symptoms: 100 to 200 mg 3 or 4 times/day	Children ≥12 years of age Urinary Tract Symptoms: 100 to 200 mg 3 or 4 times/day	Tablet: 100 mg
Oxybutynin	Bladder Instability: Tablet/Syrup (IR): 5 mg two to three times/day; maximum, 5 mg four times/day Overactive Bladder: Tablet (ER): 5 to 10 mg once daily; maximum, 30 mg/day Transdermal gel: the contents of one sachet should be applied once daily Transdermal patch: one 3.9 mg/day system applied twice weekly (every 3 to 4 days)	The safety and effectiveness of the transdermal formulations have not been established in pediatric patients. Children ≥5 years of age: Bladder Instability: Tablet/Syrup (IR): 5 mg two times a day; maximum, 5 mg three times/day Children ≥6 years of age: Detrusor Overactivity Associated with a Neurological Condition: Tablet (ER): 5 mg once daily; maximum, 20 mg/day	Syrup: 5 mg/5 ml Tablet (IR): 5 mg Tablet (ER): 5 mg 10 mg 15 mg Transdermal gel: 10% Transdermal patch: 3.9 mg/24 hours
Solifenacin	Overactive Bladder: 5 to 10 mg once daily	The safety and effectiveness have not been established in pediatric patients.	Tablet: 5 mg 10 mg
Tolterodine	Overactive Bladder: Tablet (IR): 2 mg twice daily Capsule (ER): 4 mg once daily	The safety and effectiveness have not been established in pediatric patients.	Capsule (ER): 2 mg 4 mg Tablet (IR): 1 mg 2 mg
Trospium	Overactive Bladder: Tablet (IR): 20 mg twice daily Capsule (ER): 60 mg once daily	The safety and effectiveness have not been established in pediatric patients.	Capsule (ER): 60 mg Tablet: 20 mg

ER=extended-release, IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the genitourinary smooth muscle relaxants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Genitourinary Smooth Muscle Relaxants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chapple et al.[23] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	RCT, DB, PG, MC (Pooled analysis of data from 3 studies) Men and women aged ≥18 years with symptoms of OAB for ≥6 months, 5–50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 h) and urgency (a mean of ≥1 episode/24 h)	N=1,059 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of significant leaks/week, voiding frequency, bladder capacity, frequency and severity of urgency, number of nocturnal awakenings caused by OAB, responder rates, proportion of patients experiencing three or more dry days/week, or at least 7 consecutive dry days, in the last 2 weeks of study treatment, adverse events	Primary: The median change in weekly incontinence episodes from baseline was -8.8 (-68.4%) for darifenacin 7.5 mg and -10.6 (-76.8%) for darifenacin 15 mg compared to placebo (-53.8% and -58.3%; P=0.004 and P<0.001 vs placebo, respectively). Secondary: There was a decrease in the number of significant leaks (P<0.001), voiding frequency (P<0.001), number/severity of urgency episodes (P<0.001), and an increase in bladder capacity (P<0.001) with both doses of darifenacin compared to placebo. There was no difference in the number of nocturnal awakenings/week caused by OAB between the darifenacin and placebo groups (P=0.13 and P=0.06 for darifenacin 7.5 mg and 15 mg, respectively). The proportion of patients who achieved a ≥70% reduction from baseline in the number of incontinent episodes/week was 48% for 7.5 mg and 57% for 15 mg darifenacin, compared with 33% and 39% of patients in the placebo group (P<0.001). The proportion of patients who achieved a ≥90% reduction from baseline was 27% and 28% of patients in each of these groups, respectively, compared with 17% of patients in the placebo group (P<0.005). The odds ratios for improvement compared with placebo were consistent for both doses across all responder rates analyzed (odds ratio 1.8–1.9 for 7.5 mg and 1.8–2.2 for 15 mg darifenacin; P<0.005). Responder rates for the reduction in urgency episodes also showed significant differences from placebo (P<0.05) for both doses of darifenacin at all levels of response (≥30%, ≥50%, ≥70%, ≥90%). The proportion of patients who attained a normal voiding frequency (<8 voids/day) after 12 weeks of treatment was significantly greater with both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				doses of darifenacin (7.5 mg, 34%; P=0.029 vs placebo; and 15 mg, 35%; P=0.007 vs placebo) than in the corresponding placebo groups (27% and 28%, respectively). Twenty-four percent of patients treated with darifenacin 15 mg were 'dry' for at least 7 days, compared with 16% in the corresponding placebo group (P=0.011). More patients (55% and 61%) had ≥3 dry days/week in the darifenacin 7.5 mg and 15 mg groups, respectively, than in those taking placebo (43% and 48%, respectively, both P<0.001). The overall incidence of adverse events (AEs) of any cause was 54% with darifenacin 7.5 mg and 65.6% with 15 mg darifenacin compared to 48.7% with placebo. The most common all-cause AEs were dry mouth and constipation, most of which were mild to moderate. The incidence of nervous system AEs reported by patients taking 7.5 mg or 15 mg of darifenacin was comparable to placebo. The most common nervous system AEs were CNS-related: dizziness (darifenacin 7.5 mg, 0.9%; 15 mg, 2.1%; vs placebo 1.3%) and somnolence (0.3% and 0.9% vs 0.8%, respectively). The incidence of all-cause cardiovascular AEs with darifenacin 7.5 mg (6.2%) or 15 mg (3.6%) was also comparable with that of placebo (2.3%).
Foote et al.[24] (2005) Darifenacin ER 7.5 to 15 mg once daily vs placebo	RCT, DB, PG, MC (Pooled analysis of data from 3 studies) Men and women aged ≥65 years with symptoms of OAB for ≥6 months, 5–50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 h) and urgency (a mean of ≥1 episode/24 h)	N=317 12 weeks	Primary: Median change in the number of incontinence episodes/week Secondary: Number of micturitions/24 hours, bladder capacity, number of urgency episodes per 24 hours, and adverse events	Primary: At week 12, the median reduction in the number of incontinence episodes/week was significantly greater for darifenacin 7.5 mg (-11.2; -66.7%) and darifenacin 15 mg (-10.8; 75.9%) compared to placebo (-4.8; -34.8% and -6.8; 44.8%, respectively; P<0.001). Secondary: There was a significant decrease in the frequency of micturition/24 hours (P<0.001) and urgency episodes (P<0.001), and increased bladder capacity (P<0.001) with both doses of darifenacin compared to placebo. Adverse events were reported by 53.6%, 69.1% and 50.9% of patients treated with 7.5 mg darifenacin, 15 mg darifenacin or placebo. The most common treatment-related adverse events, dry mouth, constipation and dyspepsia. The incidence of nervous system and cardiovascular adverse events during darifenacin therapy was similar to that with placebo, and did

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				not increase with increasing dose of darifenacin.
Haab et al.[25] (2006) Darifenacin ER 7.5 to 15 mg once daily	OL, MC, ES Men and women aged ≥65 years who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB for ≥6 months, 5–50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 h) and urgency (a mean of ≥1 episode/24 h)	N=716 2 years	Primary: Safety, tolerability and efficacy	Primary: All-causality adverse events (AEs) were reported by 80% of patients at some time during the 2-year extension and resulted in discontinuation in 8.9% of patients. The most commonly reported AEs were dry mouth and constipation (23.3% and 20.9%, respectively). There were no relevant changes in any bowel-habit variables from feeder-study end to extension-study end in the overall group. There were few treatment-related cardiovascular and nervous system AEs; 0.4%, 0.3% and 0.3% of patients reported hypertension, arrhythmias and tachycardia, respectively, while 0.4% of patients each reported hypertonia, somnolence and paresthesia. Abnormal vision was reported in 0.6% of patients. No patient developed treatment-related glaucoma or reported worsening of a pre-existing glaucomatous condition. After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (84.4%), voids/24 hours was -1.4 (-13.9%), urgency episodes/24 hours was -3.9 (-56.4%), severity of urgency was -15.4 (-28.8%), nocturnal awakenings for OAB/week was -1.5 (-14.3%), and significant leaks/week was -4.7 (-100%). All variables were P<0.001 vs feeder study baseline. Overall, 62.3% of patients achieved a ≥70% reduction in incontinence episodes and 43.8% achieved a ≥90% reduction at 2 years.
Hill et al.[26] (2007) Darifenacin ER 7.5 to 15 mg once daily	OL, MC, ES Men and women aged ≥18 years who had completed one of two RCTs (feeder studies) who had previously had symptoms of OAB	N=214 2 years	Primary: Safety, tolerability and efficacy	Primary: Dry mouth and constipation were the most common treatment-related (adverse events) AEs in this older patient population (23.4% and 22.4%, respectively) and were associated with low discontinuation rates (2.3% and 4.2%, respectively). Treatment-related cardiovascular and peripheral/CNS AEs were infrequently reported (1.4% and 3.3%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	for ≥6 months, 5–50 episodes of incontinence/week, and a high voiding frequency (a mean of ≥8 voids/24 h) and urgency (a mean of ≥1 episode/24 h)			After 24 months of treatment with darifenacin, the median change from baseline of the feeder studies in incontinence episodes/week was -11.0 (83.7%), voids/24 hours was -1.2 (-12.4%), urgency episodes/24 hours was -3.7 (-52.0%), severity of urgency was -12.6 (-23.3%), nocturnal awakenings for OAB/week was -1.4 (-10.9%), and significant leaks/week was -4.9 (-100%). All variables were P<0.001 vs feeder study baseline. There were high proportions of responders by all definitions (≥50%, ≥70% or ≥90% reductions in incontinence episodes/week), with 74.1%, 60.0% and 44.4%, patients age ≥65 years of age achieving these response levels at 24 months, respectively. Thirty-four percent of older patients experienced normalization of micturition (<8 micturitions/day) after 3 months of darifenacin treatment and this effect was maintained in approximately the same number of patients at the end of the 2-year study (33.8%).
Zinner et al.[78] (2005) Darifenacin ER 15 to 30 mg once daily for 14 days vs oxybutynin IR 5 mg three times daily for 14 days vs placebo for 14 days	RCT, DB, PC, XO Patients 18 to 85 years of age with urge incontinence with ≥4 significant incontinent episodes/week (defined as leakage that would normally require a change of clothing or absorbent pad) and urinary frequency ≥8 voids/24 hours	N=76 2 weeks	Primary: Incontinence episodes/week, urgency episodes/day, severity of urgency episodes, and micturitions/day	Primary: The mean number of incontinence episodes/week decreased from 20.4 to 10.93 with solifenacin 15 mg (P<0.05 vs placebo), 8.82 with solifenacin 30 mg (P<0.05 vs placebo), 9.45 with oxybutynin (P<0.05 vs placebo), and 14.64 with placebo. The mean number of urgency episodes/day decreased from 9.3 to 7.95 with solifenacin 15 mg (P<0.05 vs placebo), 7.59 with solifenacin 30 mg (P<0.05 vs placebo), 8.12 with oxybutynin (P<0.05 vs placebo), and 8.71 with placebo. The mean severity of urgency episodes decreased from 2.0 to 1.93 with solifenacin 15 mg (P<0.05 vs placebo), 1.84 with solifenacin 30 mg (P<0.05 vs placebo), 1.89 with oxybutynin (P<0.05 vs placebo), and 2.03 with placebo. The number of micturitions/day decreased from 10.4 to 9.93 with solifenacin 15 mg (P=NS vs placebo), 8.85 with solifenacin 30 mg (P<0.05 vs placebo), 9.24 with oxybutynin (P=NS vs placebo), and 9.62 with placebo. Dry mouth occurred in a similar percentage of patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				darifenacin 30 mg and oxybutynin, which was significantly higher than treatment with placebo or darifenacin 15 mg (P<0.05). There was no significant difference between darifenacin 15 mg and placebo. Constipation occurred more frequently with darifenacin and oxybutynin than placebo. There was no significant difference between darifenacin 15 mg and oxybutynin. Blurred vision and dizziness occurred in 3.3% and 1.6% of patients receiving oxybutynin, respectively.
Chapple et al.[32] (2005) <u>Cohort 1</u> Darifenacin IR 2.5 mg three times daily (t.i.d.) for 7 days vs oxybutynin 2.5 mg three times daily (t.i.d.) for 7 days <u>Cohort 2</u> Darifenacin ER 15 mg once daily for 7 days vs oxybutynin 5 mg three times daily for 7 days <u>Cohort 3</u> Darifenacin ER 30 mg once daily for 7 days	RCT, DB, XO Patients aged 18–75 years with detrusor overactivity within the previous 6 months (either idiopathic or neurogenic with ≥2 associated symptoms (average of ≥7 micturitions/day, ≥7 episodes of urgency/week, ≥1 urge incontinence episode/week necessitating change of clothing or pads)	N=65 7 days	Primary: Urodynamic parameters, salivary flow, tolerability and safety	Primary: All urodynamic pressure parameters significantly decreased from baseline after 7 days' therapy with each treatment. No significant differences between treatments were observed for any dose of darifenacin versus oxybutynin. There were no differences between treatments in responder rates for any of the ambulatory urodynamic parameters. Reduction in salivary flow was significantly less with darifenacin ER (15 mg and 30 mg) than with oxybutynin (5 mg t.i.d.). Salivary flow was comparable for darifenacin IR (2.5 mg t.i.d.) and oxybutynin (2.5 mg t.i.d.). The mean maximum decrease in salivary flow from baseline to day 7 was significantly greater with oxybutynin 5 mg t.i.d. than with darifenacin ER 15 mg (P<0.01). There were no differences in mean heart rate for darifenacin and oxybutynin on day 7. There were no significant differences with darifenacin and oxybutynin for visual nearpoint. The most common adverse events were dry mouth and constipation, which were generally mild or moderate in severity. Dry mouth was reported more frequently in oxybutynin-treated patients than in darifenacin-treated patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oxybutynin 5 mg three times daily for 7 days				
Nitti et al.[27] (2007) Fesoterodine ER 4 to 8 mg once daily vs placebo	RCT, DB, PC, MC Men and women ≥18 years of age with OAB syndrome for ≥6 months, urinary frequency (≥8 micturitions/24 hours) and urinary urgency (≥6 episodes during the 3-day diary period) or urgency urinary incontinence (UUI)	N=836 12 weeks	Primary: Number of micturitions/24 hours, number of UUI episodes/24 hours and treatment response Secondary: Mean volume voided/micturition, daytime micturitions, nocturnal micturitions, urgency episodes/24 hours and continent days/week	Primary: The mean change from baseline in the number of micturitions/24 hours was significantly improved with fesoterodine 4 mg (-1.61, -14.9%; P<0.001) and fesoterodine 8 mg (-2.09, -16%; P<0.001) compared to placebo (-1.08, -6.9%). The mean change from baseline in the number of UUI episodes/24 hours was significantly improved with fesoterodine 4 mg (-1.65, -67.4%; P<0.001) and fesoterodine 8 mg (-2.28, -81.8%; P<0.001) compared to placebo (-0.96, -40%). Subject-reported treatment response rates with fesoterodine 4 mg (64%) and fesoterodine 8 mg (74%) were significantly higher than those with placebo (45%) at study end point (P<0.001). Secondary: Fesoterodine 4 mg showed significant improvements in the mean change from baseline compared with placebo for the number of nocturnal micturitions (P<0.05), urgency episodes (P<0.001) and continent days/week (P<0.001). Fesoterodine 8 mg was significantly better than placebo for MVV/micturition, number of urgency episodes, number of daytime micturitions and continent days/week (each P<0.001. Treatment-emergent adverse events (AEs) occurred in 55%, 61% and 69% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively. Dry mouth was the most commonly reported AE. It was usually mild to moderate in severity and it occurred in 7%, 16% and 36% of patients receiving placebo, and 4 and 8 mg fesoterodine, respectively.
Chapple et al.[28]	RCT, DB, PC, AC,	N=1,135	Primary:	Primary:

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(2007) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	MC Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 urgency urinary incontinence (UUI)/24 hours, and self-reported perception of moderate problems using a Likert scale	12 weeks	Micturitions/24 hours and treatment response Secondary: Mean volume voided/micturition, daytime micturitions/24 hours, nocturnal micturitions/24 hours, urgency episodes/24 hours, continent days/week, adverse events	The mean number of micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.73, -13.8%; P=0.001 vs placebo), fesoterodine 4 mg (-1.76, -16.7%; P<0.001 vs placebo), and fesoterodine 8 mg (-1.88, -18.6%; P<0.001 vs placebo). Treatment with tolterodine resulted in significantly greater proportion of patients who responded to treatment compared to placebo (P<0.001). The proportion of patients reporting a positive treatment response was significantly greater among patients receiving tolterodine (72%; P<0.001) fesoterodine 4 mg (75%; P<0.001) and fesoterodine 8 mg (79%; P<0.001) compared to placebo (53%). The mean reduction from baseline in UUI episodes/24 hours was significantly greater for patients receiving tolterodine (-1.74, -70%; P=0.008 vs placebo), fesoterodine 4 mg (-1.95, -80%; P=0.001 vs placebo), and fesoterodine 8 mg (-2.22, -87.5%; P<0.001 vs placebo). Secondary: Active treatment significantly increased MVV from baseline (P≤0.002) compared to placebo. The increases in MVV were 2.5, 3.0, and 3.6 times greater than placebo in the patients receiving tolterodine, fesoterodine 4 mg, or fesoterodine 8 mg, respectively. The mean number of daytime micturitions/24 hours was significantly reduced from baseline in patients receiving tolterodine (-1.35, -13.6%; P=0.003), fesoterodine 4 mg (-1.37, -14.3%; P=0.001), and fesoterodine 8 mg (-1.48, -16.9%; P<0.001) compared to placebo (-0.60, -9.5%). The mean number of nocturnal micturitions/24 hours did not differ significantly from placebo in patients receiving tolterodine (-0.40, -25%; P=0.815), fesoterodine 4 mg (-0.39, -28.6%; P=0.982), and fesoterodine 8 mg (-0.39, -23.1%; P<0.896). The mean number of urgency episodes/24 hours was significantly reduced from baseline in patients receiving tolterodine (-2.03, -16%; P=0.004), fesoterodine 4 mg (-1.88, -17.6%; P=0.002), and fesoterodine 8 mg (-2.36,

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				-19.1%; P<0.001) compared to placebo (-1.07, -11.1%). Significant improvements in change from baseline compared with placebo in number of continent days/week were observed in patients receiving fesoterodine 4 mg or 8 mg. The most frequent adverse event (AE) was dry mouth, which was mild to moderate in most patients; however, 3% of patients receiving fesoterodine 8 mg reported severe dry mouth.
Chapple et al.[29] (2008) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo (Only the results of fesoterodine ER 8 mg vs tolterodine ER 4 mg are reported)	RCT, DB, PC, AC, MC (Post-hoc analysis; Chapple 2007) Men and women ≥18 years of age with a medical history of OAB symptoms with urinary urgency for ≥6 months, ≥8 micturitions/24 hours, and either ≥6 urgency episodes or ≥3 urgency urinary incontinence (UUI)/24 hours, and self-reported perception of moderate problems using a Likert scale	N=1,135 12 weeks	Primary: Number of micturitions/24 hours and treatment response Secondary: Mean volume voided/micturition, urgency episodes/24 hours, continent days/week, HRQoL (KHQ and ICIQ-SF), adverse events	Primary: There was no significant difference in the number of micturitions/24 hours or rate of treatment response reported with tolterodine 4 mg or fesoterodine 8 mg. Fesoterodine 8 mg led to a significant improvement in UUI episodes/24 hours compared to tolterodine 4 mg in 'incontinent patients' (P<0.001). Secondary: Fesoterodine 8 mg led to a significant improvement in MVV/void in 'all patients' and 'incontinent patients' compared to tolterodine (P<0.05). Fesoterodine 8 mg led to a significant improvement in continent days/week (P<0.05) and severe urgency episodes/24 hours (P<0.05) in 'incontinent patients' compared to tolterodine 4 mg. There was no significant difference in the median percent change in number of urgency episodes/24 hours reported in 'all patients' and 'incontinent patients' with fesoterodine 8 mg or tolterodine 4 mg. Scores from the KHQ and ICIQ-SF showed a significant improvement in HRQoL for the groups treated with fesoterodine 8 mg and tolterodine 4 vs placebo. The fesoterodine 8 mg dose produced significant improvements on eight of the nine domains assessed compared to placebo. Tolterodine-treated patients reported significant improvements in six of nine KHQ domains compared to placebo. Both fesoterodine 8 mg and tolterodine 4 mg treatment resulted in a ≥5-point improvement from baseline (which constitutes a meaningful change for the patient) for all domains except

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				General Health. A major improvement in the severity of bladder-related problems from baseline to the end of treatment was reported by 39% of fesoterodine 8 mg and 34% of tolterodine 4 patients (P=0.01 for both groups vs placebo), compared with 25% on placebo. Adverse events reported in ≥2% of patients in the active-treatment groups and occurring more frequently than placebo included dry mouth, constipation, dry eye, dry throat, and elevated levels of alanine aminotransferase. More patients treated with fesoterodine 8 mg had dry mouth than those receiving tolterodine 4 mg or placebo. Most cases of dry mouth were mild or moderate; 3% of patients on fesoterodine 8 mg reported severe dry mouth. More patients on fesoterodine 8 mg reported constipation than those receiving tolterodine 4 or placebo; most cases were mild to moderate. Overall, 3.2% of patients discontinued the study prematurely because of an adverse event: placebo, 2%; tolterodine 4 mg, 3%; fesoterodine 8 mg, 5%.
Kelleher et al.[30] (2008) Fesoterodine ER 4 to 8 mg once daily vs tolterodine ER 4 mg once daily vs placebo	RCT, DB, PC, MC (Pooled analysis of 2 trials) Men and women aged ≥18 years with OAB syndrome for ≥6 months	N=1,971 12 weeks	Primary: Treatment-related effects on HRQoL using the KHQ (disease-specific questionnaire to assess LUTS), ICIQ-SF (questionnaire to evaluate patients with UI including urinary frequency, urine leakage and perceived impact of these symptoms on patients' daily lives) and a six-point Likert Scale used by patients to rate the severity of problems related to	Primary: The fesoterodine 8 mg group had statistically significant improvements over placebo in eight of nine KHQ domains. Fesoterodine 4 mg and tolterodine showed statistically significant improvements over placebo in seven of nine domains of the KHQ. Fesoterodine 8 mg led to better results than 4 mg in two domains (Emotions and Severity/Coping; P<0.05). There were no significant differences between fesoterodine 8 mg and tolterodine 4 mg. In all treatment groups, all but one KHQ domain (General Health) showed improvements meaningful to the patient (i.e., changes of ≥5 points from baseline). All active-treatment groups reported a significant improvement in the ICIQ-SF score vs placebo (P<0.001). There were no significant differences between active treatment groups. Baseline scores for the six-point Likert scale were 3.6, which indicates moderate to severe problems. At the end of the study, the scores were 2.3 to 2.8, which indicates minor problems. The percentage of patients reporting scores of 1–3 was <1% at baseline and increased after 12 weeks. There was also a similar change in scores with placebo. A major improvement in bladder condition (i.e., ≥2-point change) was reported by

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			their bladder condition, and treatment response	33% of patients on fesoterodine 4 mg, 38% on fesoterodine 8 mg, and 34% on tolterodine compared to 21% on placebo (P<0.001). The percentage of patients reporting a positive treatment response was significantly higher in those receiving fesoterodine than those receiving placebo. There were significant differences between the doses in favor of fesoterodine 8 mg at 2 weeks and 12 weeks.
Wyndaele et al.[31] (2009) Fesoterodine ER 4 to 8 mg once daily	OL, MC Men and women aged ≥18 years with self-reported OAB symptoms for ≥3 months, mean micturition frequency of ≥8 micturitions/24 hours, mean number of urgency episodes ≥3/24 hours, and treated with tolterodine or tolterodine ER for OAB within 2 years who reported being 'somewhat dissatisfied' or 'very dissatisfied' with tolterodine treatment on the Treatment Satisfaction Question (TSQ)	N=516 12 weeks	Primary: Number of micturitions, number of UUI episodes, number of micturition-related urgency episodes/24 hours, and the percentage of patients reporting treatment satisfaction at week 12 ('very satisfied' or 'somewhat satisfied' on the TSQ) Secondary: Change from baseline to week 12 in nocturnal micturitions, severe micturition-related urgency episodes, frequency-urgency sum/24 hours, change from baseline in PPBC,	Primary: The change from baseline to week 12 in the number of micturitions was -3.0 (-22%; P<0.0001), -1.7 for the number of UUI episodes (-100%; P<0.0001), and -5.0 for urgency episodes (-57%; P<0.0001), At 12 weeks, 80% of patients who responded to the TSQ reported being satisfied with fesoterodine treatment, with 38.4% of patients being 'very satisfied' and 41.4% of patients being 'somewhat satisfied'. Secondary: The change from baseline to week 12 in the number of nocturnal micturitions was -0.8 (-31%; P<0.0001), -3.5 for severe urgency episodes (-94%; P<0.0001), and -15.2 for frequency-urgency sum/24 hours (P<0.0001). Mean PPBC scores improved from 4.9 at baseline to 3.1 at week 12 (P<0.0001). Mean UPS scores improved from 1.8 at baseline to 2.4 at week 12 (P<0.0001). The mean change in OAB-q Symptom Bother score (29-point improvement) from baseline to week 12 was statistically significant (P<0.0001). Mean changes in total HRQL (26-point improvement) and all four HRQL domain (Concern, 29-point improvement; Coping, 31-point improvement; Sleep, 25-point improvement; Social Interaction, 17-point improvement) scores were also significant at 12 weeks, compared with baseline (P<0.0001). The improvements for all scales and domains were above the

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			UPS and OAB-q scores at week 12	minimally important difference of 10 points, indicating that these changes were clinically meaningful. Dry mouth (23%) and constipation (5%) were the most frequently reported adverse events (AEs).
Anderson et al.[33] (1999) Oxybutynin ER 5 to 30 mg daily vs oxybutynin IR 5 mg 1-4 times/day	RCT, MC, DB, AC Community dwelling men and women with urge incontinence or mixed incontinence with a primary urge component who had at least 6 urge incontinence episodes a week when not taking medication (who had previously responded to oxybutynin)	N=97 Not specified	Primary: Urge incontinence episodes/week Secondary: Proportion of participants achieving elimination of urge incontinence episodes, number of incontinence episodes, proportion of those achieving continence, adverse events	Primary: The mean number of weekly urge incontinence episodes decreased from 27.4 to 4.8 in the extended-release group and from 23.4 to 3.1 in the immediate-release group (P=0.6). The percentage reduction in weekly urge incontinence episodes was 84% in the extended-release group and 88% in the immediate-release group (P=0.71). Secondary: Of the participants, 52% in the extended-release group and 51% in the immediate-release group had no urge incontinence episodes at the end of treatment (P=0.7). Total incontinence (urge, stress and other) episodes decreased from 29.3 to 6 in the extended-release group and from 26.3 to 3.8 in the immediate-release group from baseline to the end of the study (P=0.6). The percentage reduction in any incontinence episodes was 82% in the extended-release group and 88% in the immediate-release group (P=0.5). The proportions of patients who were totally continent was 41% in the extended-release group and 40% in the immediate-release group (P=0.9). Normal void frequency increased 54% in the extended-release group and 17% in the immediate-release group (P<0.001). At least one anticholinergic event occurred in 87% of patients in the extended-release group and 94% of patients in the immediate-release group. The most common anticholinergic event in both groups was dry mouth (68% of the extended-release group and 87% of the immediate-release group; P=0.04). Fewer participants reported moderate or severe dry mouth with extended-release oxybutynin (25% versus 46%, P=0.03). There was no significant difference among the treatment groups for other anticholinergic adverse events. There were few reports of moderate to

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				severe dry mouth at the 5 mg dose, and there was a trend in both groups toward increasing frequency of dry mouth as doses increased.
Barkin et al.[34] (2004) Oxybutynin ER 15 mg daily vs oxybutynin IR 5 mg three times daily	RCT, DB, PG, MC Men and women >18 years of age with urge urinary incontinence (UI) who demonstrated >7 UI episodes/week and >8 voids/day	N=123 9 weeks	Primary: Void frequency, UI episodes, treatment-related changes in quality of life (QoL) as assessed by the Incontinence Impact Questionnaire (IIQ) and Urogenital Distress Inventory (UDI), and adverse events	Primary: The mean number of incontinence episodes/week decreased from 24.3 to 10.4 in the extended-release group (P<0.001 vs baseline) and from 23.0 to 6.1 in the immediate-release group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.404). The mean voluntary micturition episodes/day decreased from 11.4 to 9.6 in the extended-release group (P<0.001 vs baseline) and from 11.0 to 8.6 in the immediate-release group (P<0.001 vs baseline). There was no significant difference among the treatment groups (P=0.286). There was no significant difference among the treatment groups in mean urine voided/micturition (P=0.533), incidence of urgency (P=0.116), or severity of urgency (P=0.255). There was a significant reduction from baseline in the mean number of pads/day in the extended-release group (2.3. to 1.7; P<0.001); however, there was no change from baseline in the immediate-release group (2.4 to 1.9; P=NS). Patients in both treatment groups demonstrated significant improvements from baseline in mean IIQ scores (ER P<0.001; IR P<0.001) and mean UDI scores (ER P<0.001; IR P<0.001). There were no significant differences among the treatment groups. The most frequently reported adverse events in the ER and IR oxybutynin groups were dry mouth (68% and 72%, respectively) and dry throat (31% and 37%, respectively). There was no significant difference in the incidence of moderate and severe dry mouth among the treatment groups (ER 26% and IR 42%). More patients in the ER group rated their medication tolerable compared with the IR group (P=0.020). More patients discontinued treatment in the IR oxybutynin group than in the ER oxybutynin group (P=0.047), primarily due to adverse events.
Birns et al.[35] (2000)	RCT, DB, PC, MC	N=130	Primary: Proportion of	Primary: At the completion of the study, 53% of patients receiving oxybutynin ER

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Oxybutynin ER 10 mg once daily vs oxybutynin IR 5 mg twice daily	Patients aged 18-76 years with detrusor instability or detrusor hyperreflexia whose symptoms were stabilized on conventional oral oxybutynin tablets (5mg twice daily) for 2 weeks	6 weeks	patients with daytime continence at completion of the study Secondary: Percentage of patients with nighttime continence, median change in the number of voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study, adverse events	were continent during the day compared to 58% of patients receiving oxybutynin IR (P=0.62). Secondary: There was no significant difference between the treatment groups in the percentage of patients with nighttime continence at the completion of the study or the median change in the number of voluntary daytime voids, voluntary nighttime voids, daytime episodes of incontinence and nighttime episodes of incontinence from the week preceding treatment to the completion of the study. Dry mouth and vision abnormalities were more common in patients receiving oxybutynin ER than in those receiving oxybutynin IR; however, this was not significant (P=NS).
Versi et al.[36] (2000) Oxybutynin ER 5 to 20 mg/day vs oxybutynin IR 5 to 20 mg/day	RCT, DB, MC, PG Patients with 7 to 45 urge incontinence episodes/week and ≥4 days of incontinence/week who had previously responded to treatment with anticholinergic	N=226 Not specified	Primary: Number of incontinence episodes and total incontinence episodes	Primary: Urge incontinence episodes decreased from 18.6 to 2.9/week with oxybutynin ER (83% reduction; P<0.001) and from 19.8 to 4.4/week with oxybutynin IR from baseline (76% reduction; P<0.001). There was no significant difference between the treatment groups (P=0.36). Total incontinence episodes decreased from 20.2 to 3.5/week with oxybutynin ER (81% reduction; P<0.001) and from 22.4 to 5.4/week with oxybutynin IR from baseline (75% reduction; P<0.001). There was no significant difference between the treatment groups (P=0.41).

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	drugs			There was no significant difference in anticholinergic adverse events among the treatment groups. Dry mouth occurred in 47.7% and 59.1% of patients receiving oxybutynin ER and IR, respectively.
Nilsson et al.[37] (1997) Oxybutynin ER 10 mg daily for 60 days vs oxybutynin IR 5 mg twice daily for 60 days	XO Female patients 37 to 65 years of age with symptoms of urge incontinence and detrusor instability	N=17 120 days	Primary: Frequency of voluntary voiding, the maximal volume of urine/single void, and the total volume of voluntarily voided urine/24 hr	Primary: The frequency of voids/24 hr was reduced by 23% with oxybutynin ER and by 24% with oxybutynin IR (P=0.51). Treatment with oxybutynin ER resulted in a 28% reduction in the total weight of pads compared to a 21% reduction with oxybutynin IR (P=0.80). The total volume of voluntary voided urine/day increased by 15% with both treatments (P=0.75), and the maximal volume of urine/void increased by 26% and 34% with oxybutynin ER and oxybutynin IR, respectively (P=0.95). There were no significant differences in adverse events among the treatment groups, including dry mouth (P=0.41), headache (P=1.00), dyspepsia (P=0.26), or vision abnormality (P=0.32).
Davila et al.[38] (2001) Oxybutynin transdermal 2-4 patches applied twice weekly vs oxybutynin IR 5-7.5 mg orally two or three times daily The dose of oxybutynin was initiated and	RCT, DB, MC, PC Patients ≥18 years of age with a history of urge or mixed urinary incontinence with a predominance of urge symptoms who had symptomatic improvement during a minimum of 6 weeks of oral oxybutynin	N=76 6 weeks	Primary: Average number of daily incontinence episodes, patient-completed visual analog scale for efficacy, dry mouth on an anticholinergic symptoms questionnaire, cystometric comparisons	Primary: The average daily incontinence episodes were reduced by approximately 5 episodes in both groups (P<0.0001), with no significant difference between transdermal and oral therapy. The change in the mean visual analog scale score for each group was 5.8 versus 6.0 cm for the transdermal and oral groups, respectively (P<0.0001). The difference in mean visual analog scale score between transdermal and oral therapy was 0.1 cm (P=0.9). Dry mouth occurred in 38% of patients in the transdermal group compared with 94% of patients in the oral group (P<0.001). Blurred vision, dizziness, drowsiness, palpitations, nausea and impotence were comparable between the groups. Average bladder volume at first detrusor contraction increased by 66 ml in the transdermal (P<0.0055) and 45 ml in the oral groups (P=0.1428). There was no significant difference among the transdermal and oral

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titrated based on previous oxybutynin therapy and tolerance to study medication.				groups (P=0.57). Average maximum cystometric capacity increased 53 ml and 51 ml in the transdermal (P<0.0011) and the oral (P<0.0538) groups, respectively. Post-void residual volume increased by an average of 13 ml and 16 ml in the oral and transdermal groups, respectively (P=NS). The most frequent treatment related adverse events were dry mouth, constipation, somnolence, dizziness, blurred vision and impaired urination, which occurred more frequently in the oral group.
Appell et al.[39] (2001) OBJECT Oxybutynin ER 10 mg daily vs tolterodine IR 2 mg twice daily	RCT, DB, PG, MC Participants with OAB who had between 7 and 50 episodes of urge incontinence/week and 10 or more voids/24 hours	N=378 12 weeks	Primary: Number of urge incontinence episodes/week, number of total incontinence episodes/week and micturition frequency episodes/week	Primary: The number of urge incontinence episodes/week decreased from 25.6 to 6.1 in the oxybutynin group and from 24.1 to 7.8 in the tolterodine group (P=0.03). The number of total incontinence episodes/week decreased from 28.6 to 7.1 in the oxybutynin group and from 27.0 to 9.3 in the tolterodine group (P=0.02). Micturition frequency episodes/week decreased from 91.8 to 67.1 in the oxybutynin group and from 91.6 to 71.5 in the tolterodine group (P=0.02). Both drugs improved symptoms of overactive bladder significantly from baseline to the end of the study as assessed by the 3 main outcome measures (P<0.001). Overall, 92.6% and 95.3% of the patients in the oxybutynin and tolterodine groups, respectively, had fewer incontinence episodes at the end of the study period compared to baseline. The incidence of dry mouth was similar among the treatment groups (28.1% for oxybutynin and 33.2% for tolterodine; P=0.32). Moderate to severe dry mouth was also similar among the treatment groups (10.2% for oxybutynin and 10.9% for tolterodine; P=0.87). Other adverse events were similar among the treatment groups. Overall, the discontinuation rates for adverse events were 7.6% in the oxybutynin group and 7.8% in the

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				tolterodine group (P=0.99).
Sand et al.[40] (2004) Oxybutynin ER 10 mg once daily vs tolterodine IR 2 mg twice daily	RCT, DB Women with urge or mixed incontinence (≥7 and ≤50 urge incontinence episodes/week and ≥10 voids/24 hours	N=315 12 weeks	Primary: Number of urge incontinence episodes, total incontinence, micturition frequency, tolerability	Primary: The number of urge incontinence episodes decreased from 28.1 to 6.2/week in the oxybutynin ER group compared to a reduction from 28.9 to 8.5/week in the tolterodine IR group (P=0.038). Total incontinence episodes decreased from 25.2 to 7.3/week in the oxybutynin ER group compared to a reduction from 25.1 to 10.1/week in the tolterodine IR group (P=0.030). Micturition frequency decreased from 91.7 to 68.0/week in the oxybutynin ER group compared to a reduction from 91.6 to 71.2/week in the tolterodine IR group (P=0.272). There was no significant difference in dry mouth, central nervous system events or other adverse events among the treatment groups.
Diokno et al.[41] (2003) OPERA Oxybutynin ER 10 mg daily vs tolterodine ER 4 mg daily	RCT, DB, MC, AC Women ≥18 years of age with OAB who documented 21-60 urge urinary incontinence (UUI) episodes/week and ≥10 voids/day	N=790 12 weeks	Primary: Mean weekly UUI episodes, weekly total incontinence episodes and weekly micturition frequency, adverse events	Primary: The mean weekly episodes of UUI decreased from 37.1 to 10.8 in the oxybutynin group and from 36.7 to 11.2 in the tolterodine group (P=0.28). The mean number of total incontinence episodes decreased from 43.4 to 12.3 in the oxybutynin group and from 42.4 to 13.8 in the tolterodine group (P=0.08). Patients receiving oxybutynin had a greater decrease in the mean weekly micturition frequency compared with tolterodine participants (P=0.003). The proportion of participants who reported total dryness (no incontinence episodes) in their last 7-day 24-hour voiding diary was 23.0% in the oxybutynin group compared to 16.8% in the tolterodine group (P=0.03). The proportion of participants who reported no UUI episodes at the last assessment was 26.7% in the oxybutynin group compared to 20.9% in the tolterodine group (P=0.06). Dry mouth was more common in the oxybutynin group than in the tolterodine group (29.7% vs 22.3%, respectively; P=0.02). Most reports of dry mouth events were mild. Other anticholinergic adverse events

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				(constipation, impaired urination-retention, and blurred vision) and central nervous system adverse effects (dizziness, somnolence, depression, and confusion) occurred at similar frequencies in each group. Adverse events led to discontinuation of study medication by 20 patients receiving oxybutynin and 19 receiving tolterodine.
Reinberg et al.[42] (2003) Oxybutynin ER 5 mg/day (titrated to response) vs tolterodine ER 2 mg/day (titrated to response) vs tolterodine IR 2 mg/day (titrated to response)	OL Pediatric patients with a history of non-neurogenic diurnal urinary incontinence and symptoms of overactive bladder	N=132 Not specified	Primary: Urinary frequency, incontinence and safety	Primary: Oxybutynin ER led to a greater reduction in urinary frequency compared to tolterodine IR (P<0.01). Both oxybutynin ER and tolterodine ER were significantly better than tolterodine IR in improving symptoms of diurnal incontinence and urinary frequency (P<0.01 and P<0.05, respectively). Oxybutynin ER was significantly more effective than tolterodine ER in completely resolving diurnal incontinence (P<0.05). There were no significant differences in the peripheral or central nervous system anticholinergic side effects among the treatment groups.
Dmochowski et al.[43] (2003) Oxybutynin transdermal delivery system (OXY-TDS) 3.9 mg/day applied twice weekly vs	RCT, DB Patients ≥18 years of age who were receiving pharmacologic treatment for OAB and who had a beneficial response to the pre-study treatment	N=361 12 weeks	Primary: Change from baseline in the number of incontinence episodes/day, average daily urinary frequency, average urinary volume/void, and changes in the quality of life instruments	Primary: There was a significant reduction in the number of urinary incontinence episodes/day in patients treated with OXY-TDS compared to placebo (median change -3 vs -2, respectively; P=0.0137). There was a significant reduction in the number of urinary incontinence episodes/day in patients treated with TOL-LA compared to placebo (median change -3 vs -2, respectively; P=0.0011). There was no significant difference between OXY-TDS and TOL-LA in the reduction of incontinent episodes (P=0.2167). The reduction in incontinence episodes corresponded to a 75% improvement in the OXY-TDS group, 75% in the TOL-LA group, and 50% in the placebo group.

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tolterodine ER (TOL-LA) 4 mg daily vs placebo				Complete continence was achieved by 39% of patients in the OXY-TDS group, 38% of patients in the TOL-LA group, and 22% of patients in the placebo group (both, P=0.014 vs placebo). The mean decrease in average daily urinary frequency was -1.9 micturitions/day with OXY-TDS (P=0.1010 vs placebo) -2.2 micturitions/day with TOL-LA (P=0.0025 vs placebo), and -1.4 micturitions/day with placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.2761). The median increases in average urinary volume/void was +24 ml with OXY-TDS (P=0.0010 vs placebo), +29 ml with TOL-LA (P=0.0017 vs placebo) and +5.5 ml in the placebo group. There was no significant difference between OXY-TDS and TOL-LA (P=0.7690). The patients' Global Assessment of Disease State scores were significantly improved with OXY-TDS (P=0.0106) and TOL-LA (P=0.0001) compared to placebo. There was no significant difference between OXY-TDS and TOL-LA (P=0.1861). The total IIQ scores improved significantly with OXY-TDS (P=0.0018) and TOL-LA (P=0.0045) compared to placebo. Significant improvements in irritative symptoms of the Urogenital Distress Inventory questionnaire were also observed with OXY-TDS (P=0.0156) and TOL-LA (P=0.0010) compared to placebo. The most common treatment-related adverse events in the OXY-TDS group were application site reactions, including erythema (8.3%) and pruritus (14.0%). Dry mouth (4.1% vs 1.7% with placebo; P=0.2678) and constipation (3.3%) were also reported. Adverse events led to treatment discontinuation in 10.7% of patients receiving OXY-TDS. Anticholinergic adverse events were the most common treatment-related events in the TOL-LA group (13%). Dry mouth occurred at a greater rate with TOL-LA (7.3%) than placebo (1.7%; P=0.0379). Constipation occurred in 5.7% of TOL-LA patients. Adverse events led to treatment discontinuation in 1.6% of patients receiving TOL-LA.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metello et al.[44] (2007) Solifenacin 5 mg once daily	OL Women ≥18 years of age with OAB symptoms (≥8 voids/24 hours and ≥1 incontinence episode/24 hours) for ≥3 months who had either not received any previous medication or who had been previously unsuccessfully treated with trospium	N=40 30 days	Primary: Patient self-assessment of improvement after 30 days using the urgency severity scale (USS) in both treatment groups Secondary: Reduction of the daily number of voids and urgency or involuntary leakage episodes	Primary: After 30 days of therapy, treatment with solifenacin led to a significant improvement in USS scores when assessed in all patients (P<0.001). There was no significant difference in USS scores among patients who were drug naïve compared to those who had previously failed trospium. Overall 16% of patients experienced no improvement, 13.5% had mild improvement and 69.5% had great improvement. Secondary: Treatment with solifenacin resulted in a significant reduction in urgency episodes, involuntary leakage episodes, and number of voids/24 hours when assessed in all patients (P<0.001). There was no significant difference in these endpoints among patients who were drug naïve compared to those who had previously failed trospium. Overall, 16% of patients had no improvement in the number of involuntary leakage episodes, 11% of patients had mild improvement and 73% of patients had great improvement. For daily urgency episodes, 13.5% of patients had no improvement, 27% had a mild reduction, and 59% had a great reduction.
Chancellor et al.[45] (2008) VERSUS Solifenacin 5 to 10 mg once daily	OL, MC Patients ≥18 years of age with symptoms of OAB for ≥3 months who had been treated with tolterodine ER 4 mg for ≥4 weeks, and wished to switch therapy because of a lack of sufficient subjective improvement in urgency (≥3	N=441 12 weeks	Primary: Change in urgency episodes compared with pre-washout (when patients were receiving tolterodine ER 4 mg) Secondary: Change in micturitions, incontinence episodes, nocturia episodes, and	Primary: The mean change in the number of urgency episodes/24 hours was −3.4 from pre-washout to study end (P<0.001). The median percent change was -75%. Secondary: The mean change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from pre-washout to study end was –1.6, –1.9, –0.7, and –0.8, respectively (all, P<0.001). The median percent change from pre-washout was –15.0% for the number of micturitions, –96.4% for incontinence episodes, – 40.8% for nocturia episodes, and – 40.0% for nocturnal voids. The median change in micturitions, incontinence episodes, nocturia episodes, and nocturnal voids from post-washout to study end was –2.0

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	urgency episodes/24 hours)		nocturnal voids compared with pre-washout and post-washout. Patient-reported outcomes (PRO) using the Patient Perception of Bladder Condition (PPBC) and the Overactive Bladder Questionnaire (OAB-q) was also assessed.	(-19.5%), –2.0 (-100%), –0.7 (-43.7%), and –0.7 (-40%), respectively (all, P<0.001). The mean PPBC score decreased from pre-washout by 1.2 points (95% CI, –1.3 to –1.1; P<0.001) and from post-washout by 1.2 points (95% CI, –1.3 to –1.0; P<0.001). Patients had significant improvements on the OAB-q at study end compared with both pre-washout and post-washout (all, P<0.001). The mean changes in OAB-q scores at study end relative to pre-washout and post-washout were –27.4 and –29.5, respectively, for symptom bother; 23.1 and 27.9 for coping; 25.2 and 29.7 for concern; 21.9 and 24.5 for sleep; 11.1 and 15.0 for social interaction; and 21.1 and 25.2 for total HRQL. The most common adverse events were dry mouth (17.5%), constipation (11.6%), and blurred vision (2.3%).
Zinner et al.[46] (2008) VERSUS Solifenacin 5 to 10 mg once daily	OL, MC Patients ≥18 years of age with OAB symptoms for ≥3 months who were previously treated with tolterodine ER 4 mg/day for ≥4 weeks, and who wished to switch to solifenacin due to lack of sufficient improvement in urgency episodes while receiving tolterodine (≥3 urgency episodes/24 hours)	N=441 12 weeks	Primary: Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP), Health Utilities Index (HUI), and a resource utilization questionnaire administered at pre-washout and week 12	Primary: Patients reported significantly fewer physician office visits (0.2 vs 1.2; P<0.0001), UTIs (0.1 vs 0.2; P<0.0001), and pads/diapers (7.9 vs 10.7/week; P=0.0009) with solifenacin compared to the pre-washout period. There were no significant differences in the numbers of skin rashes or falls reported at end of the study compared with pre-washout. Patients reported using fluid management as a behavioral management strategy on fewer days with solifenacin compared to when they were taking tolterodine ER 4 mg/day (14.2 vs 18.0 days; P=0.0381). There were no significant differences in other behavioral management strategies. Based on the WPAI-SHP, patients who were working reported a reduction in percent of work time missed (0.2% vs 2.1%; P=0.0017), a reduction in percent of impairment while working (11.3% vs 22.9%; P<0.0001), a reduction in percent of overall work impairment (11.9% vs 24.0%; P<0.0001), and a reduction in percent of activity impairment (18.4% vs 31.6%; P<0.0001) after 12 weeks of therapy with solifenacin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in the health utility score between pre-washout and end of study based on the HUI 2/3.
Wong et al.[47] (2009) Solifenacin 5 to 10 mg once daily	OL Women with OAB who had previously taken oxybutynin IR without benefit or developed intolerable adverse effects	N=9 12 weeks	Primary: Daytime frequency, nocturia, number of incontinence episodes, average urinary voided volume, and quality-of-life (OAB-q short form symptom bother)	Primary: The mean number of daytime micturitions was reduced from 11.4 to 7.3 with solifenacin (P=0.0002). The mean number of nocturia episodes was reduced from 2.8 to 0.9 with solifenacin (P=0.0004). The total number of incontinence episodes/day was reduced from 4.9 to 1.9 with solifenacin (P=0.02). The mean micturition volumes were increased from 160 to 280 ml with solifenacin (P=0.002). The symptom severity domain of the OAB-questionnaire (OAB-q) showed a value of 60.8% at baseline and 32.0% at 12 weeks with solifenacin (P=0.001). The health-related quality-of-life (HRQL) domain of the OAB-q showed a value of 45.5% at baseline and 73.3% at 12 weeks with solifenacin (P=0.0006).
Garely et al.[48] (2006) VOLT Solifenacin 5 to 10 mg once daily	OL, MC Patients ≥18 years of age with OAB (urgency, urge urinary incontinence, frequency, and/or nocturia for ≥3 months)	N=2,225 12 weeks	Primary: Patient Perception of Bladder Condition (PPBC) scale, overactive bladder questionnaire (OAB-q), and a visual analog scale (VAS) for the degree of bother caused by individual OAB symptoms	Primary: The mean PPBC scale score decreased significantly to 2.9 (mean change, -1.4; 95% CI, -1.49 to -1.38; P<0.001), which corresponded to a perception of "some minor problems" associated with their bladder condition. There were significant improvements in all of the OAB-q scoring domains (symptom severity, coping, concern, sleep, social interaction, and overall HRQoL) with solifenacin (all subscales, P<0.001). Significant improvements in urinary urgency, urge urinary incontinence, frequency, or nocturia were observed with solifenacin on the VAS. For urinary urgency, 88.2% of patients indicated less bothersome symptoms; for urge urinary incontinence, 89.4% of patients indicated less bothersome symptoms; for frequency, 88.3% of patients indicated frequency was less bothersome; for nocturia, 87.5% of patients indicated that nocturia was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				less bothersome. Anticholinergic adverse events occurred as follows: dry mouth (21.4%), constipation (13.3%), headache (3.4%), blurred vision (2.6%), nausea (1.8%), dyspepsia (1.5%), and dry eyes (1.3%). A total of 9.7% of patients discontinued treatment due to an adverse event. The most frequently reported treatment-emergent AEs that resulted in discontinuation were dry mouth (1.9%) and constipation (1.9%).
Haab et al.[49] (2005) Solifenacin 5 to 10 mg once daily	OL, ES Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours) for >3 months	N=1,633 40 weeks	Primary: Safety and tolerability Secondary: Efficacy	Primary: Dry mouth occurred in 10% of patients receiving solifenacin 5 mg and 17% of patients receiving solifenacin 10 mg. The discontinuation rate due to dry mouth was 0.4%. After 40 weeks, 85% of patients indicated satisfaction with solifenacin tolerability, and 99% of patients rated solifenacin tolerability as either ‘‘satisfactory’’ or ‘‘acceptable.’’ Secondary: The mean number of urgency episodes/24 hours decreased by 63%. For patients with ≥1 episode of urgency/24 hours at baseline, 40% had no symptomatic urgency at end point. The mean number of incontinence episodes/24 hours decreased by 66%. For patients with ≥1 episode of incontinence at baseline, 58% were continent at end point. The mean number of micturitions/24 hours decreased by 2.97 (23%) with solifenacin. A total of 39% of patients had <8 micturitions/24 hours by study end. The mean number of nocturia episodes/24 hours decreased by 32% and the mean volume voided/micturition increased by 31%.
Chapple et al.[50] (2006) Solifenacin 5 to 10 mg once daily	RCT, DB, MC, PC (Pooled analysis of 4 studies) Patients ≥18 years	N=2,848 12 weeks	Primary: Urgency episodes (mean absolute values and median percentage values),	Primary: Treatment with solifenacin 5 mg and 10 mg resulted in a -2.9 (-66.1%) and -3.4 (-70.0%) reduction in urgency episodes, respectively, compared to a -2.0 (-40.0%) reduction with placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	of age with OAB (≥8 micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or a mean of ≥1 urgency episode/24 hours)		incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume voided/micturition	Treatment with solifenacin 5 mg and 10 mg resulted in a -1.5 (-100%) and -1.8 (-100%) reduction in incontinence episodes, respectively compared to a -1.1 (-63.6%) reduction with placebo (P<0.001). The frequency of micturition was significantly reduced with solifenacin 5 mg (-2.3; -19.4%) and 10 mg (-2.7; -22.5%) compared to placebo (-1.4; -12.0%; P<0.001). The number of nocturia episodes were significantly reduced with solifenacin 5 mg (-0.6; -35.5%) and 10 mg (-0.6; -36.4%) compared to placebo (-0.4; -25.0%; P<0.05 and P<0.001 for solifenacin 5 mg and 10 mg, respectively). The volume voided/micturition increased significantly with solifenacin 5 mg (32.3 ml; 19.0%) and 10 mg (42.5 ml; 25.7%) compared to placebo (8.5 ml; 3.1%; P<0.001). The most common adverse events were dry mouth, constipation, and blurred vision. The incidence of dry mouth was higher in the 10 mg solifenacin group compared to the 5 mg group. The numbers of patients discontinuing treatment due to adverse events were are follows: 4.4%, 2.8%, and 6.8% with placebo, solifenacin 5 mg and solifenacin 10 mg.
Abrams et al.[51] (2005) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (Pooled analysis of 4 studies) Subgroup of patients >18 years of age with symptoms of OAB (≥8 micturitions/24 hours or ≥1 urgency episode/24 hours) who did not experience incontinence episodes at baseline	N=975 12 weeks	Primary: Urgency episodes, micturition frequency, and nocturia episodes/24 hours, and volume voided/micturition	Primary: The mean change from baseline in urgency episodes/24 hours (-3.2, -3.2, -2.1), micturition frequency/24 hours (-2.6, -2.8, -1.6), and volume voided/micturition (24.9 ml, 33.9 ml, 7 ml) were significantly greater with solifenacin 5 mg and 10 mg than placebo, respectively (all P<0.001). The mean change from baseline in nocturia episodes/24 hours was significantly greater for solifenacin 10 mg than placebo (P<0.01). The percentage of patients with resolution of urgency (36.6%, 32.9%, 24.6%) and normalization of micturitions (29%, 34.7%, 18.5%) was significantly greater with solifenacin 5 mg and solifenacin 10 mg compared to placebo, respectively (P<0.05 to P<0.001). The percentage of patients with resolution of nocturia (14.1%, 20.9%, 12.8%) was significantly greater with solifenacin 10 mg compared to placebo (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Dry mouth was reported in 3.6%, 10.8%, and 24.4% of patients receiving placebo, 5 mg solifenacin, and 10 mg solifenacin, respectively. The incidence of constipation was 1.3%, 4.0%, and 12.2% with placebo, 5 mg, and 10 mg, respectively. Discontinuations due to adverse events for the solifenacin 5 mg group (2.8%) and solifenacin 10 mg group (7.8%) were comparable with or less than that of the placebo group (6.2%).
Millard et al.[52] (2006) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (Pooled analysis of 4 studies) Subgroup of patients ≥18 years of age with severe OAB (>3 incontinence episodes/24 hour, >8 urgency episodes/24 hours, or >13 micturition episodes/24 hours)	N=472 to 787 12 weeks	Primary: Responder rates, urgency episodes, incontinence episodes, micturition, frequency, nocturia episodes/24 hours, and volume voided/micturition	Primary: For those with >3 incontinence episodes/24 hours, the percentage of patients who were continent at study end point was significantly higher with solifenacin 5 mg (28.4%; P<0.01) and 10 mg (30.5%; P<0.001) compared to placebo (15.3%). The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.01) and 10 mg (P<0.001) than with placebo. For those with >8 urgency episodes/24 hours, the percentage of patients with resolution of urgency at study end point was significantly higher with solifenacin 5 mg (12.4%, P<0.01) and 10 mg (13.9%, P<0.001) compared to placebo (4.6%). The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 10 mg compared to placebo (P<0.001). For solifenacin 5 mg, the mean change for all efficacy parameters was significantly greater than placebo (P<0.05; except micturition frequency/24 hours). For those with >13 micturitions/24 hours, the percentage of patients who achieved normalization of micturition frequency (<8 micturitions/24 h) at study end point was significantly higher with solifenacin 10 mg (13.3%, P<0.001) compared to placebo (4.0%). There was no significant difference between solifenacin 5 mg and placebo. The mean change in the number of episodes of incontinence and urgency, the frequency of micturitions and volume voided/micturition was significantly greater with solifenacin 5 mg (P<0.05) and 10 mg (P<0.001) compared to placebo. The incidence of adverse events was comparable among the treatment groups. Dry mouth, constipation, urinary tract infection, blurred vision,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and nausea occurred at a higher incidence with solifenacin 5 or 10 mg than with placebo. Discontinuations due to adverse events occurred in 4.1%, 7.5%, and 4.8% of patients in the solifenacin 5 and 10 mg and placebo groups, respectively.
Wagg et al.[53] (2006) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (Pooled analysis of 4 RCT and 1 OL extension study) Subgroup of patients ≥65years of age with OAB (≥8 micturitions/24 hours, and either a mean of ≥1 incontinence episode/24 hours or a mean of ≥1 urgency episode/24 hours)	N=1,554 12 to 40 weeks	Primary: Urgency episodes (mean absolute values and median percentage values), incontinence episodes, micturition frequency, nocturia episodes/24 hours, and volume voided/micturition	Primary: In the 12-weeks studies, elderly patients had significantly greater decreases in the mean number of incontinence episodes/24 hours with solifenacin 5 mg and 10 mg compared to placebo (P=0.013 and P<0.001, respectively). The median change in the number of incontinence episodes/24 hours was -1.0 (-92.4%) and -1.5 (-91.9%) with solifenacin 5 mg and 10 mg, respectively, and -0.7 (-50%) with placebo (P<0.001 for 10 mg dose). There was no significant difference between solifenacin 5 mg and placebo. A greater percentage of elderly patients who were incontinent at baseline were continent with solifenacin 5 mg and 10 mg (49.1% and 47.3%, respectively) compared to placebo (28.9%; P<0.001). In 12-week studies, elderly patients had significantly greater decreases in the mean number of urgency episodes/24 hours with solifenacin 5 mg and 10 mg compared to placebo (P<0.001). The median change in the number of urgency episodes was -2.3 (-76.1%) and -2.7 (-66.7%) with solifenacin 5 mg and 10 mg, respectively, and -1.5 (-33.3%) with placebo (P<0.001 for 10 mg dose). A greater percentage of elderly patients with urgency at baseline had resolution of urgency with solifenacin 5 mg and 10 mg (34.6% and 24.9%, respectively) compared to placebo (16.9%; P<0.001 for 5 mg and P<0.01 for 10 mg). In 12-week studies, elderly patients had significantly greater decreases in the mean number of micturitions/24 hours with solifenacin 5 mg and 10 mg compared to placebo (P<0.001). The median change in the number of micturitions was -2.0 (-18.3%) and -2.3 (-22%) with solifenacin 5 mg and 10 mg, respectively, and -1.0 (-10.3%) with placebo (P=0.008 for the 5 mg dose and P<0.001 for the 10 mg dose. In 12-week studies, elderly patients had a significantly greater increase in the mean volume voided/micturition with solifenacin 5 mg and 10 mg compared to placebo (P<0.001).The median change in volume voided/micturition was 27.2 (17.8%) and 40.1 (28.5%) f with solifenacin 5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg and 10 mg, respectively, and 6.2 (3.7%) with placebo (P<0.001). During the 40-week extension trial, elderly patients maintained improvements in the number of incontinence episodes/24 hours, urgency episodes/24 hours, and number of micturitions/24 hours, and experienced an increase in the volume voided/micturition compared with baseline. A total of 59.5% of elderly patients were continent and 37.8% reported resolution of urgency at the end of the study period. During the 12-week trials, the most commonly reported adverse events were dry mouth, constipation, and urinary tract infection. Rates of discontinuation were 5.5% in the placebo group, 4.7% in the solifenacin 5 mg group, and 9.3% in the solifenacin 10 mg group. During the 40-week extension, the most common adverse events were dry mouth, constipation, and urinary tract infection. A total of 9.2% of patients discontinued therapy due to any type of adverse event.
Kelleher et al.[54] (2005) Solifenacin 5 to 10 mg once daily vs placebo	RCT, DB, MC, PC (Pooled analysis of 2 RCT and 1 OL extension trial) Patients ≥18 years of age with symptoms of OAB (≥8 micturitions/24 hours and either ≥1 urgency episode/24 hours or ≥1 incontinence episode/24 hours) for >3 months	N=3,237 12 to 40 weeks	Primary: QoL data using the King's Health Questionnaire (KHQ)	Primary: In the 12-weeks studies, there was a significant improvement in all QoL domains (except personal relationships) with solifenacin compared to placebo (P<0.05 to P<0.001). In the 40-week extension study, there was a significant improvement in all QoL domains with solifenacin (17% for the general health perception and 35-48% for all the other domains).
Chapple et al.[55] (2004) Solifenacin 2.5 to 20 mg once daily	RCT, DB, PC Patients 18 to 80 years of age with OAB and	N=225 6 weeks	Primary: Number of voids/24 hours Secondary:	Primary: The mean change in number of voids/24 hours was significantly lower with solifenacin 5 mg (-2,21), 10 mg (-2.47) and 20 mg (-2.75) compared to placebo (-1.03; all P<0.05). There was no significant difference with tolterodine (-1.79) compared to placebo (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 4 weeks vs tolterodine IR 2 mg twice daily for 4 weeks vs placebo for 4 weeks	urodynamic evidence of detrusor overactivity (>8 voids/24 h and >3 episodes of incontinence or urgency)		Volume voided/ void; incontinence episodes/24 hours; urgency episodes/24 hours; and total sum score of Contilife items 1-27, sum scores of the five Contilife domains (i.e., daily activities, effort, self-image, emotional consequences, and sexuality), and overall Contilife QoL score	Secondary: The mean volume voided/void was significantly greater for solifenacin 5 mg, 10 mg and 20 mg than for placebo (all P<0.01). There was no significant difference with tolterodine compared to placebo. There was no significant difference in the mean number of incontinence episodes/24 hours with solifenacin or tolterodine compared with placebo. There was no significant difference in the number of urgency episodes/24 hours with solifenacin or tolterodine compared to placebo. Treatment with solifenacin led to significant improvements over baseline based on the results of the Contilife sum score QoL analysis compared with placebo. There was no significant difference with tolterodine compared to placebo. Treatment with solifenacin led to significant improvements in the daily life activities (all groups, P<0.01), self-image (10 mg and 20 mg, P<0.05), emotional consequences (5 mg, 10 mg and 20 mg, P<0.05) and sexuality (10 mg and 20 mg, P<0.05) compared to placebo. Tolterodine resulted in significant improvements in the daily life activities domain only compared to placebo (P<0.05). Solifenacin 10 mg and 20 mg and tolterodine produced significant improvements over placebo in the Contilife overall QoL score (P<0.05). The most frequently reported adverse event was dry mouth, followed by constipation and blurred vision. The frequency of dry mouth was highest among patients receiving solifenacin 20 mg (38%), tolterodine 2 mg (24%) and solifenacin 5 mg and 10 mg (14% each). Constipation was reported in 19% of patients taking solifenacin 20 mg.
Chapple et al.[56] (2004) Solifenacin 5 to 10 mg once daily	RCT, DB, MC Patients ≥18 years with symptoms of OAB (including	N=1,081 12 weeks	Primary: Urgency episodes, all incontinence episodes, urge incontinence	Primary: There was a significant decrease in the mean number of urgency episodes/24 hours with solifenacin 5 mg and 10 mg (-52% and -55%, respectively) compared to placebo (-33%; both P<0.001). There was no significant difference in urgency episodes/24 hours between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tolterodine IR 2 mg twice daily vs placebo	urgency, urge incontinence, or frequency) for ≥3 months (≥8 voids/24 h, ≥3 episodes of urgency and/or ≥3 episodes of incontinence)		episodes, voids/24 hours and voided volume/void	tolterodine (-38%) and placebo (P=0.0511). Direct comparison of solifenacin 5 mg and 10 mg with tolterodine resulted in estimated differences of - 0.791 and - 1.015 (95% CI, -1.434 to -0.148, and -1.659 to -0.370), respectively. There was a significant decrease in urge incontinence episodes/24 hours with solifenacin 5 mg (-1.41, P=0.002) and 10 mg (-1.36, P=0.0028) compared to placebo (-0.62). There was no significant difference in urge incontinence episodes/24 hours between tolterodine (-0.91) and placebo (P=0.2390). There was no significant difference in urge incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.487; 95% CI, -0.988 to 0.014 and 10 mg, -0.436; 95% CI, -0.921 to 0.048). There was a significant decrease in all incontinence episodes/24 hours with solifenacin 5 mg (-1.42, P=0.008) and 10 mg (-1.45, P=0.0038) compared to placebo (-0.76). There was no significant difference in all incontinence episodes/24 hours between tolterodine (-1.14) and placebo (P=0.1122). There was no significant difference in all incontinence episodes/24 hours between solifenacin and tolterodine (5 mg, -0.276; 95% CI, -0.761 to 0.208 and 10 mg, -0.316; 95% CI, -0.786 to 0.164). There was a significant decrease in mean number of voids/24 hours with solifenacin 5 mg (-2.19, -17%; P<0.001), solifenacin 10 mg (-2.61, -20%; P<0.001) and tolterodine (- 1.88, -15%; P=0.0145) compared to placebo (-1.20, - 8%). Direct comparison of solifenacin 5 mg and 10 mg with tolterodine resulted in estimated differences of -0.312 and -0.737 (95% CI -0.844 to 0.219, and -1.269 to -0.204). There was a significant increase in mean volume voided/void with solifenacin 5 mg (32.9 ml, +25.1%), solifenacin 10 mg (39.2 ml, +29.0%), and tolterodine (24.4 ml, +20.3%) compared to placebo (7.4 ml; all, P<0.001). There was no significant difference in mean volume voided/void between solifenacin and tolterodine (5 mg, 8.4 ml; 95% CI, 0.496 to 16.34 and 10 mg, 14.8 ml; 95% CI, 6.855 to 22.72).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The percentages of patients discontinuing treatment for an adverse event were 3.7% in the placebo group, 3.2% in the solifenacin 5 mg group, 2.6% in the solifenacin 10 mg group, and 1.9% in the tolterodine group. The incidence of dry mouth was lowest with solifenacin 5 mg (14%). Constipation was reported in 7.2% and 7.8% of patients treated with solifenacin 5 mg and 10 mg, respectively, in 2.6% of patients treated with tolterodine and in 1.9% of placebo patients. Blurred vision was reported in 3.6% of patients receiving solifenacin 5 mg, 5.6% receiving solifenacin 10 mg, 1.5% receiving tolterodine, and 2.6% receiving placebo.
Chapple et al.[57] (2005) STAR Solifenacin 5 to 10 mg once daily vs tolterodine ER 4 mg once daily	RCT, DB, MC Patients ≥18 years of age with OAB symptoms (≥8 micturitions/24 hours, ≥1 incontinence episode/24 hours, or ≥1 urgency episode/24 hours) for ≥3 months	N=1,200 12 weeks	Primary: Micturition frequency Secondary: Urgency episodes, urge incontinence, total incontinence, nocturia, proportion of patients who experienced a 50% reduction in incontinence episodes, pad usage, and QoL using a 6-point categorical scale to assess perception of bladder condition (PBC)	Primary: The mean number of micturitions was reduced with solifenacin (-2.45) compared to treatment with tolterodine (-2.24; P=0.004 for non-inferiority). Secondary: Treatment with solifenacin led to a reduction in the number of urgency episodes/24 hours (-2.85) compared to treatment with tolterodine (-2.42, P<0.05). Treatment with solifenacin led to a reduction in the number of urge incontinence episodes/24 hours (-1.42) compared to treatment with tolterodine (-0.83, P<0.01). Treatment with solifenacin led to a reduction in the number of total incontinence episodes/24 hours (-1.60) compared to treatment with tolterodine (-1.11, P<0.01). There was no significant difference in nocturia among the treatment groups (P=0.730). Approximately 74% of patients receiving solifenacin who were incontinent at baseline experienced ≥50% reduction in incontinence episodes compared to 67% of patients receiving tolterodine (P=0.021). The percentage of patients who were incontinent at baseline who became continent at study end point was 59% (solifenacin) and 49% (tolterodine; P=0.006). The mean volume voided/micturition increased with solifenacin (38 ml)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared with tolterodine (31 ml; P=0.010). Solifenacin decreased the number of incontinence pads used compared to tolterodine (P=0.0023). Patient-reported PBC was significantly improved with solifenacin compared to tolterodine (P=0.006). Approximately 5.9% of patients receiving solifenacin and 7.3% of patients receiving tolterodine discontinued treatment (for any reason); 1.2% and 2.0% discontinued therapy due to insufficient therapeutic response with solifenacin and tolterodine, respectively. The most common adverse events were dry mouth, constipation and blurred vision. The percentage of patients discontinuing treatment due to adverse events was similar between the treatment groups (3.5% of patients receiving solifenacin and 3.0% of patients receiving tolterodine). A total of 1.2% and 2.0% of patients discontinued therapy due to an insufficient therapeutic response with solifenacin and tolterodine, respectively.
Lee et al.[58] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	RCT, DB, MC, PG Patients ≥18 years of age with OAB and symptoms of urinary urgency and frequency (≥8 micturitions/24 hour) for ≥6 months	N=228 8 weeks	Primary: Number of micturition/24 hours and incontinence episodes/24 hours	Primary: The number of micturitions/24 hours decreased with tolterodine (-2.6) and oxybutynin (-1.8) compared to baseline. There was no significant difference among the treatment groups (P=0.14). In patients who were incontinent at baseline, the number of incontinence episodes/24 hours decreased with tolterodine (-2.2) and oxybutynin (-1.4). There was no significant difference among the treatment groups (P=0.10). Overall, 45% of patients who received tolterodine and 46% of patients who received oxybutynin reported ‘much’ benefit. There was no significant difference among the groups. The most frequently reported adverse events were autonomic nervous system disorders, gastrointestinal disorders, and urinary disorders. Dry mouth was the most commonly reported adverse event and was significantly higher with oxybutynin than tolterodine (P=0.001). There was a higher frequency of moderate-to-severe dry mouth with oxybutynin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(28%) than tolterodine (9%).
Malone-Lee et al.[59] (2001) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg twice daily	RCT, DB, MC Patients ≥50 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 h)	N=379 10 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition	Primary: The number of micturitions/24 hours decreased with tolterodine (-1.7) and oxybutynin (-1.7). There was no significant difference among the treatment groups (P=0.97). The number of incontinence episodes/24 hours decreased with tolterodine (-1.3) and oxybutynin (-1.8). There was no significant difference among the treatment groups (P=0.065). The change in volume voided/micturition increased with tolterodine (+33 ml) and oxybutynin (+34 ml). There was no significant difference among the treatment groups (P=0.90). Approximately 45% of patients treated with tolterodine and 41% treated with oxybutynin perceived improvement after 12 weeks of treatment. There was no significant difference among the treatment groups. Autonomic nervous system disorders and gastrointestinal problems were the most commonly reported adverse events. A higher percentage of patients experienced dry mouth with oxybutynin (61%) than with tolterodine (37%). Severe dry mouth was more common in the oxybutynin group (15%) than in the tolterodine group (4%). The proportion of patients who withdrew because of adverse events was similar in the oxybutynin group (15%) and in the tolterodine group (15%).
Appell et al.[60] (1997) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR	RCT, DB, MC, PC (Pooled analysis of 4 trials) Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours) and urge	N=1,120 12 weeks	Primary: Number of micturitions/24 hours, number of incontinence episodes/24 hours, and mean urinary volume voided/micturition	Primary: The number of micturitions/24 hours significantly decreased with tolterodine 1 mg (P<0.001), tolterodine 2 mg (P<0.001), and oxybutynin (P<0.01) compared to placebo. There was no significant difference between tolterodine 2 mg and oxybutynin. The number of incontinence episodes/24 hours significantly decreased with tolterodine (1 mg and 2 mg) and oxybutynin compared to placebo (P<0.05). There was no significant difference between tolterodine 2 mg and oxybutynin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 mg three times daily vs placebo	incontinence (≥1 incontinence episode/24 hours) or urinary frequency			The change in volume voided/micturition significantly increased with tolterodine (1 mg and 2 mg) and oxybutynin compared to placebo (P<0.001). Approximately 39% of patients who received placebo, 41% treated with tolterodine 1 mg, 52% treated with tolterodine 2 mg (P=0.003 vs placebo), and 50% treated with oxybutynin (P=0.017 vs placebo) perceived improvement after 12 weeks of treatment. Dry mouth was the most common adverse event (16% of the placebo group, 24% of the tolterodine 1 mg group, 40% of the tolterodine 2 mg group, and 78% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in the oxybutynin group than in the tolterodine or placebo groups (all, P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (60%) compared to the tolterodine 1 mg group (4%), tolterodine 2 mg group (17%), and placebo group (6%; all, P<0.001). Other commonly reported adverse events included headache, dyspepsia, dizziness, and UTI. Dyspepsia was reported at a higher rate with oxybutynin (11%) than with tolterodine2 mg (6%; P=0.006). The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group than in either of the tolterodine groups or the placebo group (all, P<0.001).
Abrams et al.[61] (1998) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily	RCT, DB, MC, PC Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 h) for ≥6	N=293 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition	Primary: The mean change in number of micturitions/24 hours was significantly lower with tolterodine (-2.7; P=0.0022) compared to placebo (-1.6). There was no difference between oxybutynin (-2.3) and placebo (P=0.068). There was also no significant difference between tolterodine and oxybutynin (95% CI, -1.1 to 0.1). The number of incontinence episodes/24 hours significantly decreased with oxybutynin (-1.7; P=0.023) compared to placebo (-0.9). There was no difference between tolterodine (-1.3) and placebo (P=0.22). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.2 to 1.0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	months			The change in volume voided/micturition significantly increased with tolterodine (+38 ml) and oxybutynin (+47 ml) compared to placebo (+6 ml; P<0.001). Approximately 47% of patients who received placebo, 50% treated with tolterodine, and 49% treated with oxybutynin perceived improvement after 12 weeks of treatment. There was no significant difference among the groups. Dry mouth was the most common adverse event. It was reported at a significantly higher rate with both tolterodine (50%) and oxybutynin (86%) than placebo (21%; P<0.001). It was also more common with oxybutynin than tolterodine (P<0.001). The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (17%) than in the tolterodine (8%) or placebo (12%) groups.
Drutz et al.[62] (1999) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily vs placebo	RCT, DB, MC, PC Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 h)	N=277 12 weeks	Primary: Number of micturition/24 hours, incontinence episodes/24 hours and volume voided/micturition	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.0; P=0.036) compared to placebo (-1.1). There was no difference between oxybutynin (-2.0) and placebo (P=0.066). There was also no significant difference between tolterodine and oxybutynin (95% CI, -0.8 to 0.8). The number of incontinence episodes/24 hours was not significantly different with tolterodine (-1.7; P=0.063) or oxybutynin (-1.7; P=0.10) compared to placebo (-1.0). There was no significant difference between tolterodine and oxybutynin (95% CI, -0.7 to 0.7). The change in volume voided/micturition significantly increased with tolterodine (+34 ml; P=0.0075) and oxybutynin (+50 ml; P=0.0001) compared to placebo (+12 ml). Dry mouth was the most common adverse event (15% of the placebo group, 30% of the tolterodine group, and 69% of the oxybutynin group). The percentage of patients reporting dry mouth was significantly higher in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the oxybutynin group than in the tolterodine group (P<0.001). The percentage of patients reporting moderate or severe dry mouth was higher in the oxybutynin group (44%) compared to the tolterodine group (9%), and placebo group (7%). Other more commonly reported adverse events with oxybutynin were headache (10%) and dizziness (11%). Headache occurred in 15% of patients receiving tolterodine. The proportion of patients who withdrew because of adverse events was higher in the oxybutynin group (31%) than in the tolterodine (13%) or placebo (14%) groups.
Leung et al.[63] (2002) Tolterodine IR 2 mg twice daily vs oxybutynin IR 5 mg three times daily	RCT, DB, MC Women ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 h)	N=106 10 weeks	Primary: Tolerability Secondary: Efficacy	Primary: The median drug compliance rate was 87.5% with oxybutynin and 75% in with tolterodine (P=0.778). Adverse events occurred in 49.1% of patients treated with oxybutynin and 60.4% of patients treated with tolterodine (P=0.329). The proportion of patients who withdrew was 15.1% with oxybutynin and 17.0% with tolterodine (P=1.0). Secondary: There was no significant difference in frequency of micturition (P=0.965), urgency episodes (P=0.672), incontinence episodes (P=0.993), or pad use (P=0.665) among the treatment groups.
Giannitsas et al.[64] (2004) Tolterodine IR 2 mg twice daily for 6 weeks vs oxybutynin IR 5 mg three times daily for 6 weeks	RCT, OL, XO Patients ≥18 years of age with OAB who were categorized according to the characteristics of the first overactive detrusor contraction during filling cystometrogram: high volume–low	N=128 12 weeks	Primary: Volume voided/micturition, number of micturition/24 hours, incontinence episodes/24 hours, and other urodynamic parameters in the total population and individual severity groups	Primary: <u>Total Study Population</u> The mean volume voided/micturition was significantly increased with tolterodine (+40.6 ml) and oxybutynin (+43.8 ml) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -0.8 with oxybutynin (which reached statistical significance only with tolterodine). There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	pressure (grade-group I), high volume–high pressure (grade-group II), low volume–low pressure (grade-group III) and low volume–high pressure (grade-group IV)			Overactivity index was significantly decreased with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There was a significant increase in bladder volume at first desire to void with tolterodine and oxybutynin, which was significantly higher with oxybutynin. The volume at first overactive detrusor contraction and maximum cystometric capacity were significantly increased with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. <u>Low volume–High pressure Overactivity (Group IV)</u> The mean volume voided/micturition was significantly increased with tolterodine (+39.7 ml) and oxybutynin (+54.2 ml) and there was no significant difference among the treatment groups. The mean change in number of micturitions/24 hours was -0.9 with tolterodine and -1.0 with oxybutynin; there was no significant difference among the treatment groups. There was an increase in the 24 hour volume of urine with both treatments; however it was only statistically significant with oxybutynin. Overactivity index was significantly decreased with oxybutynin. Volume at first desire to void was significantly increased with oxybutynin and volume at first overactive contraction was significantly increased with tolterodine. There was no significant change in pressure of first overactive contraction with tolterodine or oxybutynin. <u>Low volume–Low pressure Overactivity (Group III)</u> The mean volume voided/micturition was significantly increased with tolterodine (+48.8 ml) and oxybutynin (+43.1 ml) and there was no significant difference among the treatment groups. There were no significant changes in the rest of voiding diary parameters in this group. Overactivity index was significantly reduced with tolterodine only.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Volume at first desire to void was increased significantly with tolterodine and oxybutynin; there was no significant difference among the treatment groups. There were no significant changes for pressure of first overactive contraction and cystometric capacity with tolterodine or oxybutynin. <u>High volume–High pressure Overactivity (Group II)</u> Changes in clinical parameters did not reach statistical significance. Overactivity index was reduced by tolterodine and oxybutynin; there was no significant difference among the treatment groups. Oxybutynin achieved an increase in volume at first desire to void and volume at first overactive contraction. There were no significant changes in max cystometric capacity and pressure of first overactive contraction. <u>High volume–Low pressure Overactivity (Group I)</u> The small number of patients in this group did not allow for statistical analyses to be performed.
Harvey et al.[65] (2001) Tolterodine IR 1 to 2 mg twice daily vs oxybutynin IR 2.5 to 5 mg three times daily	MA Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours), and symptoms of urgency and/or urge incontinence (≥1 episode/24 h)	4 trials 12 weeks	Primary: Incontinent episodes/24 hours, quantity of pad used/24-hour period, micturitions/24 hours, and voided volume/micturition Secondary: Adverse events	Primary: The mean change in number of micturitions/24 hours was not significantly different between tolterodine and oxybutynin (WMD, 0.00; 95% CI, -0.38 to 0.38). The number of incontinence episodes/24 hours significantly favored oxybutynin compared to tolterodine (WMD, 0.41; 95% CI, 0.04 to 0.77). The change in volume voided/micturition significantly favored oxybutynin (–8.24 ml; 95% CI, –14.11 to –2.38). This translates to an average increase in the volume voided/micturition of more than 8 ml among patients using oxybutynin compared with patients using tolterodine. Secondary: Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.54; 95% CI, 0.48 to 0.61), including moderate to severe dry mouth (RR, 0.33; 95% CI, 0.24 to 0.45). There were fewer patients who withdrew from studies due to dry mouth with tolterodine compared to oxybutynin (RR, 0.63; 95% CI, 0.46 to 0.88).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Homma et al.[66] (2003) Tolterodine ER 4 mg once daily vs oxybutynin IR 3 mg three times daily vs placebo	RCT, DB, MC, PC, AC Patients ≥20 years of age with OAB and symptoms of urinary urgency, urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥5 episodes/week) for ≥6 months	N=608 12 weeks	Primary: Incontinence episodes/week Secondary: Voids/24 hours and mean volume voided/void, median number of incontinence pads used/24 hours, patient perception of bladder condition, patient perception of urgency, and QoL using the King's Health Questionnaire (KHQ)	Primary: The number of incontinence episodes/24 hours was significantly decreased with tolterodine (median -78.6%; P=0.0027) and oxybutynin (median -76.5%; P=0.0168) compared to placebo (-46.4%). There was no significant difference between tolterodine and oxybutynin (P=0.4469). Secondary: The number of voids/24 hours decreased with tolterodine (-2.0, P<0.001) and oxybutynin (-2.1, P=0.0114) compared to placebo (-1.1). There was no significant difference among the treatment groups (P=0.3132). The volume voided/void increased significantly with tolterodine (17.2 ml, P=0.0086) and oxybutynin (22.3 ml, P<0.001) compared to placebo (6.6 ml). The number of pads used/24 hours was not significantly different among the treatment groups. Approximately 72% of patients treated with tolterodine and 73% treated with oxybutynin perceived improvement after 12 weeks of treatment compared to 59% of patients treated with placebo. The difference between tolterodine and placebo was not significant (P=0.515). There was no significant difference between tolterodine and oxybutynin (P=0.9394). Significantly more patients reporting at least some benefit with tolterodine (79%; P=0.0091; little benefit 36%; much benefit, 42%) and oxybutynin (81%; P<0.001; little benefit 29%; much benefit 53%) than with placebo (66%; little benefit 40%; much benefit 25%). There was no significant difference between tolterodine and oxybutynin in the assessment of treatment benefit (P=0.2240). Treatment with tolterodine and oxybutynin resulted in significantly greater mean reductions in both the incontinence impact domain and role limitation domain scores (KHQ questionnaire) compared with placebo. There was no significant difference between the improvements with tolterodine and oxybutynin for either domain. Tolterodine and oxybutynin were associated with improvements in other KHO domains, including

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				physical limitations, social limitations, personal relationships, sleep/energy, severity measures, and the severity of urinary symptoms compared to placebo. The differences in improvements between tolterodine and oxybutynin were not significant for any of these domains. Dry mouth was the most common adverse event reported with tolterodine (33.5%), oxybutynin (53.7%) and placebo (9.8%). Dry mouth was more common in patients receiving oxybutynin than tolterodine (P<0.001). Other adverse events occurring in >5% of patients were constipation, abdominal pain/tenderness, dyspepsia, difficulty in voiding and headache. Eye disorders occurred in significantly more patients receiving oxybutynin than tolterodine (P<0.0383). The incidence of nervous system disorders was lower in the tolterodine group (8.4%) than in the oxybutynin group (12.7%) or placebo group (11.5%). More patients on oxybutynin withdrew due to adverse events compared to tolterodine (P<0.001).
Sussman et al.[67] (2002) ACET Trial 1 Tolterodine ER 2 to 4 mg once daily Trial 2 Oxybutynin ER 5 to 10 mg once daily	RCT, OL Patients ≥18 years of age with OAB and symptoms of urinary frequency and urgency with or without urge incontinence	Trial 1 N=669 8 weeks Trial 2 N=620 8 weeks	Primary: Patient perception of bladder condition and patient assessment of treatment benefit Secondary: Physician assessment of treatment benefit	Primary: Seventy percent of patients in the tolterodine 4 mg group perceived an improvement in their bladder condition compared to 60% in the tolterodine 2 mg group, 59% in the oxybutynin 5 mg group, and 60% in the oxybutynin10 mg group (all P<0.01 vs tolterodine 4 mg). There was a greater percentage of patients who reported an improved bladder condition with tolterodine 4 mg compared to oxybutynin 10 mg (77% vs 65%; P<0.01) in those whose perception of bladder condition was moderate to severe at baseline. There was no significant difference in the perception of their bladder condition among treatment-naïve patients (P=0.11) and those who had received prior antimuscarinic therapy (P=0.11). There was no significant difference in patient assessment or physician's assessment of treatment benefit between tolterodine and oxybutynin. Dry mouth was dose-dependent in both trials (tolterodine 2 mg vs tolterodine 4 mg; P=0.09; oxybutynin 5 mg vs oxybutynin 10 mg;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.05). Patients treated with tolterodine 4 mg reported a significantly lower severity of dry mouth compared with oxybutynin 10 mg (P=0.03).
Van Kerrebroeck et al.[68] (2001) Tolterodine ER 4 mg once daily vs tolterodine IR 2 mg twice daily vs placebo	RCT, DB, MC, PC Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 h) and urge incontinence (≥5 incontinence episodes/week) for ≥6 months	N=1,529 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition, and the number of pads used/24 hours	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.0001) and tolterodine IR (-10.6; P=0.0005) compared to placebo (-6.9). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 60%; and placebo, 33%. Tolterodine ER was 18% more effective than tolterodine IR (P<0.05). The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.8; P=0.0047) and tolterodine IR (-1.7; P=0.0079) compared to placebo (-1.2). The mean change in volume voided/micturition was significantly greater with tolterodine ER (34 ml; P=0.0001) and tolterodine IR (29 ml; P=0.0001) compared to placebo (14 ml). The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.5; P=0.0145) and tolterodine IR (-0.5; P=0.0035) compared to placebo (-0.2). The most common adverse events in all treatment groups were dry mouth, constipation, and headache. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and placebo. The rate of dry mouth was 23%, 30%, and 8% for tolterodine ER, tolterodine IR, and placebo, respectively. Patients receiving tolterodine ER had 23% less dry mouth than those taking tolterodine IR (P=0.02). Discontinuation rates due to adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%).
Swift et al.[69] (2003) Tolterodine ER 4 mg once daily vs	RCT, DB, PC, MC (Subgroup analysis) Women ≥18 years of age with urinary frequency (≥8 micturitions/24 h)	N=1,235 12 weeks	Primary: Incontinence episodes/week, number of micturition/24 hours, volume voided/micturition,	Primary: The mean change in incontinence episodes/week was significantly better with tolterodine ER (-11.8; P=0.001) and tolterodine IR (-10.1; P=0.001) compared to placebo (-7.2). The difference between tolterodine ER and tolterodine IR was significant (P=0.036). The median percentage reductions in incontinence episodes/week were: tolterodine ER, 71%; tolterodine IR, 57%; and placebo, 33%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tolterodine IR 2 mg twice daily vs placebo	and urge incontinence (≥5 incontinence episodes/week) for ≥6 months		and the number of pads used/24 hours	The mean change in number of micturitions/24 hours was significantly better with tolterodine ER (-1.9; P=0.001) and tolterodine IR (-1.7; P=0.005) compared to placebo (-1.2). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in volume voided/micturition was significantly greater with tolterodine ER (37.9 ml; P=0.001) and tolterodine IR (32.5 ml; P=0.001) compared to placebo (13.3 ml). There was no significant difference between tolterodine ER and tolterodine IR. The mean change in number of pads used/24 hours was significantly lower with tolterodine ER (-0.6; P=0.001) and tolterodine IR (-0.5; P=0.001) compared to placebo (-0.2). There was no significant difference between tolterodine ER and tolterodine IR. Dry mouth, constipation, headache and urinary tract infection were the most common adverse events in all treatment groups. With the exception of dry mouth, the incidence of adverse events was comparable between active treatment and placebo. There was no significant difference in dry mouth with tolterodine ER or tolterodine IR (P=0.06). Discontinuation rates due to adverse events were similar in all the treatment groups (tolterodine ER, 5%; tolterodine IR, 5%; placebo, 6%).
Choo et al.[70] (2008) STARGATE Tolterodine ER 4 mg once daily	OL Patients ≥18 years of age with OAB who had urinary frequency (≥8 micturitions/24 hours) and urgency (≥2 episodes/24 hours) with or without urgency incontinence	N=60 12 weeks	Primary: Rate of patient-reported goal achievement (PGA) by a visual analogue scale Secondary: Changes in symptom severity, voiding diary and patient perception of bladder condition (PPBC),	Primary: The median rate of patient-reported goal achievement (PGA) was: frequency (60%; 95% CI, 46.9–63.6), urgency (60%; 95% CI, 46.2–64.9), urge incontinence (80%; 95% CI, 34.2–80.0), nocturia (50%; 95% CI, 39.4–57.6) and tenesmus (30%; 95% CI, 25.4–52.2). Secondary: The median percentage reduction in symptom severity was as follows: frequency (45%; 95% CI, 36.2–54.4), urgency (55%; 95% CI, 40.1– 60.4), urgency incontinence (71%; 95% CI, 39.2– 76.8), nocturia (52%; 95% CI, 40.2–59.7) and tenesmus (26%; 95% CI, 16.9–50.4). Patients reported that the most troublesome symptoms were daytime frequency (50%), nocturia (17.9%), urgency incontinence (16.1%),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			global impression of improvement (GII), and willingness to continue treatment	urgency (10.7%) and tenesmus (5.4%). Frequency (-2.7), urgency (-4.2), urgency incontinence (-1.0), and nocturia (-0.7) were significantly reduced with tolterodine (all, P<0.01). The mean voided volume significantly increased with tolterodine (32 ml, P=0.05). Approximately 90% of patients experienced an improvement of at least one point in their bladder condition, and 62.5% reported improvements of at least two points on the PPBC questionnaire. After 12 weeks of treatment, 53.6% of patients experienced much improvement, 39.3% experienced little improvement, and 7.1% experienced no improvement on the GII questionnaire. A total of 73.2% of patients wished to continue treatment after receiving 3 months of treatment. The most common adverse events were dry mouth (21.7%), constipation or indigestion (10%), headache (5%), urinary tract infection (3.3%) and peripheral edema (1.7%).
Appell et al.[71] (2001) Tolterodine IR 2 mg twice daily	OL, ES Patients ≥18 years of age with OAB, increased urinary frequency (≥8 micturitions/24 hours) and urge incontinence (≥1 incontinence episode/24 hours) or urinary frequency	N=854 9 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most frequently reported adverse events were autonomic nervous system disorders (31%), gastrointestinal disorders (24%) and general body disorders (26%). The most frequently report adverse event was dry mouth, which occurred in 28% of patients (19% mild, 7% moderate, 2% severe). Of those patients enrolled in the open-label trial, 30% did not complete 9 months of therapy. The most common reasons for withdrawal were adverse events (9%), lack of efficacy (6%), lot to follow-up (6%) and withdrawal of consent (4%). Secondary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.5; P=0.0001; median change -22%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-2.0; P=0.0001; median change -76%). The change in volume voided/micturition significantly increased with tolterodine (+40 ml; P=0.0001; median change +22%). Approximately 65% of patients who received tolterodine perceived improvement after 9 months of therapy.
Abrams et al.[72] (2001) Tolterodine IR 2 mg twice daily	OL, ES Patients ≥18 years of age with urinary frequency (≥8 micturitions/24 hours), urgency, and/or urge incontinence (≥1 incontinence episode/24 hours)	N=714 12 months	Primary: Number of micturitions/24 hours, number of urge incontinence episodes/24 hours, mean urine volume voided/micturition, safety	Primary: The number of micturitions/24 hours significantly decreased with tolterodine (-2.4; P=0.0001; mean change -20%). The number of urge incontinence episodes/24 hours significantly decreased with tolterodine (-1.3; P=0.0001; median change -74%). The change in volume voided/micturition significantly increased with tolterodine (+33 ml; P=0.0001; mean change +18%). Approximately 69% of patients who received tolterodine perceived improvement after 12 months of therapy. The most frequently occurring adverse events were autonomic nervous system disorders (46%), general body disorders (22%), gastrointestinal disorders (22%) and urinary disorders (18%). The most frequently report adverse event was dry mouth, which occurred in 41% of patients (27% mild, 10% moderate, 3% severe). The most common adverse events leading to withdrawal were adverse events (15%), withdrawal of consent (13%), lost to follow-up (4%) and other (6%). A total of 34 (5%) patients withdrawing from the study due to dry mouth.
Kreder et al.[73] (2002) Tolterodine ER 4 mg once daily	OL, ES Patients ≥18 years of age with urinary frequency (≥8	N=1,077 12 months	Primary: Safety and tolerability Secondary:	Primary: The most common adverse events were autonomic nervous system disorders (13.2%), gastrointestinal disorders (11.4%), general body disorders (14.5%), respiratory disorders (9.8%), urinary disorders (9.1%) and musculoskeletal disorders (6%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	micturitions/24 hours), urge incontinence (≥5 incontinence episodes/week) and urgency for ≥6 months		Efficacy	The most frequently report adverse event was dry mouth, which occurred in 12.9% of patients. Approximately 10% of patients withdrew from the study due to adverse events. The most common adverse events leading to withdrawal were dry mouth (1.8%), headache (0.8%), abdominal pain (0.8%), dizziness (0.7%), urinary tract infection (0.7%), dyspepsia (0.6%), constipation (0.6%), xerophthalmia (0.5%), and micturition disorders (0.5%). Secondary: The number of urge incontinence episodes/week was significantly decreased with tolterodine compared to baseline (median change -83%). The number of micturitions/24 hours significantly decreased with tolterodine compared to baseline (median change -21%). The change in volume voided/micturition significantly increased with tolterodine compared to baseline (median change +25%). Approximately 75% of patients who received tolterodine perceived improvement after 12 months of therapy.
Takei et al.[74] (2005) Tolterodine ER 4 mg once daily	OL, ES Japanese patients ≥20 years of age with OAB symptoms including urinary urgency, urinary frequency (≥8 micturitions/24 h) and urge incontinence (≥5 episodes/week) for ≥6 months	N=188 12 months	Primary: Safety and tolerability Secondary: Efficacy	Primary: The most common adverse event was dry mouth (33.5%). The incidence decreased during the course of the open-label extension (24.5% during the first 3 months vs 4.3% during the 6–12-month periods). Approximately 23% of patients withdrew prematurely due to adverse events (10%), lack of efficacy (8%), consent withdrawal (3.7%), lost to follow-up (0.5%) and protocol violation (0.5%). Secondary: The number of incontinence episodes/week was decreased with tolterodine (mean change -77.2%). The number of micturitions/24 hours significantly decreased with tolterodine (mean change -21.3%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The change in volume voided/micturition significantly increased with tolterodine (mean change +19.6%; P<0.0001).
Staskin et al.[75] (2004) Trospium 20 mg twice daily vs placebo	RCT, DB, PC, MC Patients with OAB	N=658 12 weeks	Primary: CNS adverse effects and daytime sleepiness using the Stanford Sleepiness Scale (SSS)	Primary: After 12 weeks of treatment, 2.5% of patients receiving placebo and 1.5% of patients receiving trospium exhibited a clinically significant increase (3 points or greater) from baseline in their SSS scores. There was no significant difference between the treatment groups. In a subgroup analysis based on age (<65 and ≥65 years of age; <75 and ≥75 years of age), there was no significant difference in SSS scores among the treatment groups. Approximately 5.8% of patients receiving trospium and 5.2% of patients receiving placebo reported at least one CNS adverse event. Somnolence was reported by 0.3% of patients receiving trospium and 0.6% of patients receiving placebo. Sedation was reported by 0.3% of patients receiving placebo and no patients reported sedation with trospium.
Halaska et al.[76] (2003) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (OXY) 5 mg twice daily	RCT, DB, MC, AC Patients ≥18 years of age with urge syndrome, urge incontinence, urge incontinence as one component of mixed incontinence, or urge incontinence due to a neurological condition (detrusor hyperreflexia)	N=358 52 weeks	Primary: Safety and efficacy	Primary: Blood chemistry, nitrogenous metabolites, uric acid, sodium and potassium, GPT and LDH were not adversely affected by either treatment. Systolic and diastolic blood pressure were unaffected by the treatments. A pulse rate of >100 beats/min was noted in 27 patients treated with TCl (10.1%) as compared with 6 patients in the OXY group (6.7%). In the TCl group at 26 and 52 weeks of treatment, 49% and 63% of the trial physicians assessed tolerability as very good, respectively. In the OXY group, the assessment by the trial physicians at the same points showed very good tolerability in 36% and 42% of patients, respectively. Appraisal by the patients led to similar results. Adverse events were observed in 64.8% of patients in the TCl group and 76.7% of patients in the OXY group. Dry mouth was the most common adverse event and was reported by 33% of patients treated with TCl and 50% of those treated with OXY. Urinary tract infection was reported by 12% of patients receiving TCl and 11% of patients receiving OXY. For the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				adverse events taken as a whole, the differences between TCl and OXY were significant with regards to time to event (P<0.01). There was also a significant difference between the two treatment groups in favor of TCl for the overall total of adverse events having probable or possible connections with the trial medication (P=0.02), for all gastrointestinal adverse events with this classification (P=0.02) and for dryness of the mouth (P<0.01). When the number of adverse events is viewed in relation to the total number of patients treated and the duration of treatment, the risk of occurrence of an adverse event/patient/week is 0.027 for TCl and 0.045 for OXY (Relative risk of 0.6 in favor of TCl). Patients treated with TCl showed increases in maximum cystometric bladder capacity of 92 ml at 26 weeks and 115 ml at 52 weeks. The OXY group showed increases of 117 ml and 119.4 ml respectively. The changes from baseline were significant in both treatment arms (P=0.001). There was no significant difference between the treatment groups. The increase in volume at the first unstable contraction was 46.0 ml with TCl and 36.7 ml with OXY. There was no significant difference between the treatment groups. There was no significant difference between the treatment groups in the volume at the first sensation to void, as well as of other urodynamic parameters. The frequency of micturition in the TCl group decreased by 1.2 micturitions/day at 2 weeks, 2.9 micturitions/day at 26 weeks and 3.5 micturitions/day at 52 weeks. In frequency of micturitions in the OXY group decreased by 1.5 micturitions/day at 2 weeks, 3.4 micturitions/day at 26 weeks and 4.2 micturitions/day at 52 weeks. Episodes of urgency in the TCl group decreased by 1.6 at 2weeks, 3.2 at 6 weeks and 3.5 at 52 weeks. In the OXY group, episodes of urgency decreased by 1.7 at 2 weeks, 3.2 at 26 weeks and 3.6 at 52 weeks. After 52 weeks of treatment, 29% and 17% of the physicians considered the therapeutic outcome for the TCl and OXY groups as ‘‘cure’’,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				respectively. The results were similar with regards to patient assessments.
Madersbacher et al.[77] (1995) Trospium (TCl) 20 mg twice daily vs oxybutynin IR (Oxy) 5 mg three times daily	RCT, DB, MC Patients with detrusor hyperreflexia	N=95 2 weeks	Primary: Maximum bladder capacity and maximum voiding detrusor pressure during micturition Secondary: Bladder compliance, residual urine, adverse events	Primary: Maximum bladder capacity in the TCl group increased significantly by 96.6 ml (P<0.001). In the Oxy group, maximum bladder capacity increased by 163.0 ml (P<0.001). There was no significant difference between the treatment groups (P=0.057). Maximum detrusor pressure during micturition decreased by 35.4 cmH_20 (P<0.001) in the TCl group and 38 cmH_20 (P<0.001) in the Oxy group. There was no significant difference between the treatment groups (P=0.63). Secondary: Bladder compliance increased by 16.96 ml/cm H_20 (P<0.001) in the TCl group and by 22.56 ml/cmH_20 in the Oxy group (P<0.001). There was no significant difference between the treatment groups (P=0.43). Residual urine increased by 76.45 ml in the TC1 group and 114.08 in the Oxy group. There was no significant difference between the treatment groups (P=0.19). There was no significant difference between the treatment groups with regards to the frequency of hyper-reflexive waves (P=0.16). There were no significant changes in blood pressure among the treatment groups. The rate of adverse events was similar in both groups. Dry mouth occurred in 54% of patients in the TCl group and 56% of patients in the Oxy group. The severity grading showed that dryness of the mouth deteriorated to 'severe' in 4% of patients receiving TC1 and 23% of patients receiving Oxy. Withdrawal from the trial occurred more frequently in patients taking Oxy (16%) than in those taking TCl (6%). The Oxy patients withdrew earlier (after an average of 7.1 days) than the TCl patients (after an average of 14.3 days).
Chapple et al.[79] (2008) Darifenacin,	MA Patients ≥18 years of age with OAB	73 trials ≥2 weeks	Primary: Incontinence episodes/day, number of	Primary: Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of incontinence episodes/day. Pooled differences in mean changes ranged from 0.4 to 1.1 incontinence

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fesoterodine, oxybutynin, solifenacin, tolterodine, trospium			micturitions/day, urgency episodes/day, volume voided/micturition, proportion of patients returning to continence, proportion of patients undergoing global improvements in their storage LUTS Secondary: Tolerability, safety, and health-related quality of life (HRQL)	episodes/day. Tolterodine 2 mg IR was not more effective than placebo; however, the 4 mg ER/IR formulations were more effective than placebo. There were no significant differences among the antimuscarinic agents with the exception of fesoterodine 8 mg/day. One study found that this agent was more effective than tolterodine ER 4 mg/day (P=0.03). Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the number of micturitions/day. Pooled differences in mean changes ranged from 0.5 to 1.3 episodes/day. Three trials favoring solifenacin 10 mg/day over tolterodine IR 4 mg/day (P=0.01). Four trials favored solifenacin 10 mg/day over solifenacin 5 mg/day (P=0.02). Otherwise, there were no significant differences among the antimuscarinic agents. Fesoterodine, propiverine, solifenacin, and tolterodine were significantly more effective than placebo with regards to the mean change in the number of urgency episodes/day (when this outcome was reported). Pooled differences in mean changes ranged from 0.64 to 1.56 episodes/day. Some trial data favored solifenacin 10 mg/day over tolterodine IR 4 mg/day (P<0.01) and solifenacin 5 mg/day over tolterodine IR 4 mg/day (P=0.01). Otherwise, there were no significant differences among the antimuscarinic agents. Antimuscarinic agents were significantly more effective than placebo with regards to the mean change in the volume voided/micturition (when this outcome was reported). Differences in pooled mean changes were 13–40 ml. Solifenacin 10 mg/day was favored over tolterodine IR 4 mg/day (P<0.01); solifenacin 10 mg/day was favored over solifenacin 5 mg/day (P<0.01); fesoterodine 8 mg/day was favored over tolterodine ER 4 mg/day (P=0.03); and oxybutynin IR 15 mg/day was favored over tolterodine IR 4 mg/day (P<0.01). The proportions of patients who had improvements in their bladder condition was significantly higher for fesoterodine 4 mg/day and 8 mg/day than for placebo (P=0.01and P=0.01, respectively). Otherwise, there were no significant differences among the antimuscarinic agents.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Compared to placebo, treatment with oxybutynin IR (15 mg/day and 7.5 to 10 mg/day) was associated with significantly higher risk of withdrawal due to any cause (P=0.04 and P<0.01, respectively). Otherwise, there was no significant difference in the proportions of patients who withdrew for any causes between active treatments and placebo. Oxybutynin IR 7.5–10 mg/day was associated with a significantly greater risk of withdrawal due to any cause than oxybutynin ER 5 mg/day (P=0.03); oxybutynin IR 7.5 to 10 mg/day was associated with a greater risk of withdrawal than tolterodine ER 4 mg/day (P<0.01) and tolterodine IR 4 mg/day (P=0.04); oxybutynin IR 15 mg/day was associated with a greater risk of withdrawal than tolterodine IR 4 mg/day P<0.01) and oxybutynin ER 15 mg/day (P=0.04). Tolterodine ER 4 mg/day was associated with a significantly lower risk of withdrawal due to an adverse event than placebo (P=0.02). Formulations associated with a significantly higher risk of withdrawal due to adverse events than placebo were as follows: oxybutynin IR 7.5–10 mg/day (P=0.01), oxybutynin IR 15 mg/day (P<0.01), and solifenacin 10 mg/day (P=0.04). Tolterodine ER 4 mg/day was associated with lower risk of withdrawal due to an adverse event compared to oxybutynin TDS 3.9 mg/day (P=0.01) and oxybutynin IR 15 mg/day (P<0.01); tolterodine IR 4 mg/day was associated with a lower risk than oxybutynin IR 15 mg/day (P<0.01); and oxybutynin ER 5 mg/day was associated with a lower risk than oxybutynin ER 15 mg/day (P=0.04). Otherwise, there were no significant differences among the antimuscarinic agents. Every antimuscarinic agent was associated with a significantly greater risk of adverse events than placebo, except tolterodine IR 2 mg/day (P=0.97) and oxybutynin TDS 3.9 mg/day (P=0.07). The pooled RR for any adverse event in comparison to placebo varied between 1.13 and 2.00. The risk of adverse events was significantly lower with tolterodine IR 2 mg/day than with oxybutynin ER 5 mg/day (P<0.01) and lower with tolterodine IR 4 mg/day than with oxybutynin IR 7.5 to 10 mg/day (P<0.01) and oxybutynin IR 15 mg/day (P<0.01). There was a higher risk of adverse events with fesoterodine 8 mg/day than with fesoterodine 4 mg/day (P=0.04) and tolterodine ER 4 mg/day (P=0.04). There was a higher risk

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of adverse events with oxybutynin IR 7.5–10 mg/day than with trospium 40 mg/day (P=0.02). Dry mouth was the most frequently reported adverse event and occurred in 29.6% of patients receiving antimuscarinic therapy compared to 7.9% of patients receiving placebo. The following adverse events were reported at statistically significantly higher levels in first-named active treatments than in second-named active treatments: blurred vision (solifenacin 10 mg/day vs solifenacin 5 mg/day, solifenacin 10 mg/day vs tolterodine IR 4 mg/day); constipation (solifenacin 5 mg/day vs tolterodine ER and IR 4 mg/day, darifenacin 15 mg/day vs tolterodine IR 4 mg/day); fatigue (tolterodine ER 4 mg/day vs fesoterodine 4 or 8 mg/day); nausea (oxybutynin IR 15 mg/day vs oxybutynin ER 15 mg/day); and vomiting (tolterodine ER 4 mg/day vs oxybutynin ER 7.5 to 10 mg/day). Significant differences in HRQL were reported for darifenacin, fesoterodine, oxybutynin TDS, solifenacin, tolterodine ER and IR, and trospium compared to placebo.
Hay-Smith et al.[80] (2009) Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium	MA Patients with OAB with or without a urodynamic diagnosis of detrusor overactivity	N=11,332 (49 trials) Variable duration	Primary: QoL, patient's observations, symptoms, objective measurements, adverse events	Primary: <u>Oxybutynin vs tolterodine (10 studies)</u> There was no significant difference between the groups in the proportion of people reporting cure/improvement (47% with tolterodine vs 44% with oxybutynin; RR, 1.06, 95% CI 0.89 to 1.26). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in the number of leakage episodes/24 hours (WMD -0.15, 95% CI -0.47 to 0.16). There was no significant difference between IR tolterodine and ER oxybutynin with regards to the change in micturitions/24 hours (WMD -0.25, 95% CI -0.61 to 0.10). There were fewer withdrawals with tolterodine therapy (7%) compared to treatment with oxybutynin (12%; RR, 0.57; 95% CI, 0.43 to 0.75). Dry mouth was significantly lower with tolterodine than oxybutynin (RR, 0.60; 95% CI, 0.54 to 0.66).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Oxybutynin vs trospium (4 studies) Two trials reported on maximum cystometric capacity and residual volume and there was no significant difference between the groups. Dry mouth was significantly lower with trospium than oxybutynin (RR 0.74;95% CI, 0.59 to 0.93). Extended (ER) versus immediate release (IR) oxybutynin (4 trials) There was no significant difference in patient's perception of improvement (1 trial). There was no significant difference between the groups in the number of leakage episodes/24 hours. There was a lower maximum cystometric capacity and larger volume at first contraction in the ER formulations; however, only volume at first contraction was significant. There was no significant difference in residual volume measured using ultrasound. There was no significant difference in withdrawals due to adverse events between IR and ER groups. Dry mouth was significantly lower with the ER preparations (RR 0.77, 95% CI 0.66 to 0.91). ER versus IR tolterodine (1 trial) There was no significant difference between the ER and IR formulations with regards to leakage episodes or micturitions/24 hours. There was no significant difference in withdrawals due to adverse events. There were fewer reports of dry mouth for those using the ER preparation. ER oxybutynin versus IR tolterodine (1 trial) There was no significant difference in the number of leakage episodes/24 hours. There was a significant difference in favor of oxybutynin for the number of micturitions/24 hours.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in the number of withdrawals due to adverse events among the treatment groups. There was no significant difference in the rate of dry mouth among the treatment groups. <u>ER tolterodine versus IR oxybutynin (1 trial)</u> The risk of dry mouth was less for those taking ER tolterodine compared to oxybutynin IR. <u>Tolterodine ER versus oxybutynin ER (2 trials)</u> There was no significant difference in change in leakage episodes or micturitions/24 hours (1 trial). There was no statistically significant difference between the groups in withdrawals due to adverse events. There was no significant difference in the rate of dry mouth among the treatment groups; however, there was clinical heterogeneity noted among the studies. One study found significantly fewer reports of dry mouth with oral ER tolterodine than oral ER oxybutynin. There was no difference in risk of dry mouth between oral ER tolterodine and transdermal ER oxybutynin.

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 abbreviations: AC=active control, CI=confidence interval, DB=double-blind, MC=multicenter, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, XO=crossover
Miscellaneous abbreviations: HRQoL=health-related quality of life, ICIQ-SF=International Consultation on Incontinence Questionnaire–Short Form, ITT=intent-to-treat, KHQ=King's Health Questionnaire, LUTS=lower urinary tract symptoms, OAB=overactive bladder, OAB-q=Overactive Bladder Questionnaire, PP=per protocol, PPBC=Patient Perception of Bladder Condition Questionnaire, SSS=Stanford Sleepiness Scale, TSQ=Treatment Satisfaction Questionnaire, UPS=Urgency Perception Scale, USS=Urinary Sensation Scale, UUI=urgency urinary incontinence, 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/prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost/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/prescription as paid at the retail pharmacy level. For branded products with little or no recent utilization data, the average cost/prescription is calculated by the average wholesale price (AWP) and the standard daily dosing/product labeling. For generic products with little or no recent utilization data, the average cost/prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage/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/Rx
$$	$31-$50/Rx
$$$	$51-$100/Rx
$$$$	$101-$200/Rx
$$$$$	Over $200/Rx

Rx=prescription

Table 9. Relative Cost of the Genitourinary Smooth Muscle Relaxants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Darifenacin	extended-release tablet	Enablex®	$$$$	N/A
Fesoterodine	extended-release tablet	Toviaz®	$$$$	N/A
Flavoxate	tablet	N/A	N/A	$$$
Oxybutynin	extended-release tablet, syrup, tablet, transdermal gel, transdermal patch	Ditropan XL®*, Gelnique®, Oxytrol®	$$$-$$$$	$-$$$
Solifenacin	tablet	Vesicare®	$$$$	N/A
Tolterodine	extended-release capsule, tablet	Detrol®, Detrol LA®	$$$$	N/A
Trospium	extended-release capsule, tablet	Sanctura®, Sanctura XR®	$$$$	N/A

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

X. Conclusions

Urinary incontinence (UI) and overactive bladder (OAB) cause both physical and psychological morbidity, as well as adversely impact quality of life.[15] Initial treatment options include lifestyle modifications (weight loss and dietary changes), behavioral therapy (bladder training, physical therapy and toileting assistance) and pharmacologic therapy.[16-17] Anticholinergic drugs with antimuscarinic effects increase bladder capacity, decrease urgency and are useful for the treatment of urge incontinence.[16] Flavoxate, oxybutynin immediate-release syrup/tablet and oxybutynin extended-release tablets are available in a generic formulation.

Several guidelines provide recommendations on the use of the genitourinary smooth muscle relaxants for the treatment of UI and OAB. Antimuscarinic agents are the primary treatment for patients with OAB symptoms (with or without urge incontinence), in addition to lifestyle modifications and behavioral therapy.[17,20-22,81,83] In general, the guidelines do not give preference to one particular agent over another.[17,21-22,81,83]

In clinical trials, the genitourinary smooth muscle relaxants have been shown to modestly improve urinary symptoms, including frequency, urgency, nocturia and incontinence episodes.[23-80] The majority of the studies were 6 to 12 weeks in duration; however, a few long-term (1 to 2 years), open-label, non-comparative studies have also been conducted. There were very few active-controlled studies found in the medical literature with flavoxate, darifenacin, fesoterodine, solifenacin or trospium. The majority of the active-controlled studies compared oxybutynin and tolterodine. Several studies have demonstrated similar efficacy with the genitourinary smooth muscle relaxants for most, but not all, of the outcomes assessed. In general, studies directly comparing immediate-release (IR) and extended-release (ER) formulations of the same drug found no differences in efficacy.[33-38,69] Studies directly comparing IR formulations of different drugs, as well as studies directly comparing ER formulations of different drugs, also demonstrated similar efficacy.[29,32,41-43,58-64,76-77] Very few studies have demonstrated greater efficacy with one genitourinary smooth muscle relaxant over another.[39-40,57,67] The use of the genitourinary smooth muscle relaxants for the treatment of UI and OAB has also been associated with an improvement in quality of life.[29-30,34,48,54-55,57,66]

Adverse events occur frequently with the genitourinary smooth muscle relaxants due to their anticholinergic effects, which often leads to discontinuation of therapy. The most common adverse events include dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness. These agents may also cause confusion or memory impairment in the elderly.[16] The incidence of adverse events varies among the agents and depends upon the formulation used (ER, IR or transdermal). Adverse events tend to be higher with the IR formulations compared to ER formulations. In general, dry mouth occurs at a higher rate with oxybutynin than with the other agents.

There is insufficient evidence to support that one brand genitourinary smooth muscle relaxant is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand genitourinary smooth muscle relaxants 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 genitourinary smooth muscle relaxant 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 Platelet-Aggregation Inhibitors
AHFS Class 201218
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I. Overview

The platelet-aggregation inhibitors play a major role in the management of cardiovascular, cerebrovascular and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes, angina, intermittent claudication, myocardial infarction, stroke and transient ischemic attack.[1-9] In addition, they are indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery.

The platelet-aggregation inhibitors exert their pharmacologic effects through several different mechanisms. Aspirin irreversibly inhibits platelet cyclooxygenase-1.[1-3,9] Inhibition of this enzyme prevents the formation of thromboxane A2 from arachidonic acid and leads to a reduction in platelet activation. Platelets produce adenosine diphosphate (ADP) in addition to thromboxane A2. The attachment of ADP to receptors on the surface of platelets causes them to aggregate. The thienopyridines (clopidogrel, prasugrel and ticlopidine) block ADP receptors, which prevents the attachment of ADP and subsequent platelet adhesion/aggregation.[1-3,6,8] Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes.[7] This stimulates platelet adenylate cyclase and increases platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels, which inhibits platelet aggregation. Cilostazol inhibits phosphodiesterase activity and suppresses the degradation of cAMP in platelets and blood vessels.[5]

The platelet-aggregation inhibitors that are included in this review are listed in Table 1. Aspirin, cilostazol, dipyridamole and ticlopidine are available in a generic formulation. Aspirin is also available over-the-counter. This review encompasses all dosage forms and strengths. This class was last reviewed in May 2008.

Table 1. Platelet-Aggregation Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aspirin	chewable tablet, delayed-release tablet, packet, rectal suppository, sustained-release tablet, tablet	Ecotrin®*‡, Stanback Analgesic®‡, Zorprin CR®	aspirin
Aspirin and dipyridamole	extended-release capsule	Aggrenox®	none
Cilostazol	tablet	Pletal®*	cilostazol
Clopidogrel	tablet	Plavix®	none
Dipyridamole	injection, tablet	Persantine®*	dipyridamole
Prasugrel	tablet	Effient®	none
Ticlopidine	tablet	N/A	ticlopidine

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the platelet-aggregation inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Platelet-Aggregation Inhibitors

Clinical Guideline	Recommendation(s)
US Preventative Services Task Force: **Aspirin for the Prevention of Cardiovascular Disease: U.S. Preventive Services Task Force Recommendation Statement[10] (2009)**	• Men aged 45 to 79 years and women 55 to 79 years should use aspirin when potential benefit of reducing myocardial infarction outweighs the potential harm of increase risk in GI hemorrhage. • There is insufficient evidence to assess the risk to benefit ratio of aspirin in patients 80 years of age and older • Aspirin is not recommended as part of CVD prevention in women younger than 55 years and men younger than 45 years.
American College of Chest Physicians (ACCP): **Primary and Secondary Prevention of Chronic Coronary Artery Disease[73] (2008)**	<u>Post-STE and NSTS ACS Treatment</u> • For patients with ACS with or without ST-segment elevation, aspirin is recommended initially (75–162 mg), and then continued indefinitely (75 mg–100 mg/d). • For patients with ST-segment elevation ACS (with or without fibrinolytic therapy), clopidogrel is recommended (300 mg loading dose for patients <75 years of age and 75 mg for patients >75 years of age) and should be continued for 2–4 weeks (75 mg/day). It is suggested that clopidogrel be continued for up to 12 months following hospital discharge. • For patients with NSTE ACS, combination therapy with aspirin (75–100 mg/d) and clopidogrel (75 mg/d) is recommended for 12 months. • For patients in whom aspirin is contraindicated or not tolerated, clopidogrel monotherapy (75 mg/d) is recommended. • For patients with symptomatic CAD, aspirin (75–100 mg/d) in combination with clopidogrel (75 mg/d) is recommended. <u>Antithrombotic Therapy After PCI</u> • For long-term treatment of patients after PCI, aspirin (75–100 mg/d) is recommended. • For patients undergoing PCI with bare metal stent placement, aspirin (75–100 mg/d) plus clopidogrel is recommended over aspirin alone. • For patients undergoing PCI with bare metal stent placement following ACS, aspirin (75–100 mg/d) plus clopidogrel (75 mg/d) for 12 months is recommended over aspirin alone. • For patients undergoing PCI with drug-eluting stents, aspirin (75–100 mg/d) plus clopidogrel (75 mg/d) is recommended for at least 12 months. Indefinite treatment beyond 1 year with aspirin plus clopidogrel is suggested if there are no bleeding or other tolerability issues. • For patients after stent placement, clopidogrel or ticlopidine is recommended over cilostazol. Clopidogrel is recommended over ticlopidine. • For aspirin-intolerant patients undergoing PCI, the use of a thienopyridine derivative rather than dipyridamole is recommended. <u>Congestive Heart Failure Without CAD</u> • In patients with congestive heart failure due to a non-ischemic etiology, the routine use of aspirin is not recommended. <u>Antithrombotic Therapy in Patients With Saphenous Vein and Internal Mammary Bypass Grafts</u> • For all patients with coronary artery disease undergoing CABG, aspirin (75-100 mg/d) is recommended indefinitely. • For patients undergoing CABG, the addition of dipyridamole to aspirin

Clinical Guideline	Recommendation(s)
	therapy is not recommended. • For patients with coronary artery disease undergoing CABG who are allergic to aspirin, clopidogrel (300 mg as a loading dose 6 hours after operation) is recommended, followed by 75 mg/d indefinitely. • In patients who undergo CABG following NSTE ACS, clopidogrel (75 mg/d) is recommended for 9 to 12 months following the procedure in addition to treatment with aspirin. • For patients who have received clopidogrel for ACS and are scheduled for CABG, clopidogrel should be discontinued for 5 days prior to the scheduled surgery. • For all patients with coronary artery disease who undergo internal mammary artery bypass grafting, aspirin (75 to 162 mg/d) is recommended indefinitely. <u>Primary Prevention of Cardiovascular Events</u> • For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%), aspirin (75–100 mg/d) is recommended over either no antithrombotic therapy or VKA. • For all patients, the routine addition of clopidogrel to aspirin therapy is not recommended for primary prevention. For patients with an aspirin allergy who are at moderate to high risk for a cardiovascular event, monotherapy with clopidogrel is recommended. • For women <65 years of age who are at risk for an ischemic stroke, and in whom the concomitant risk of major bleeding is low, aspirin (75–100 mg/d) is suggested over no aspirin therapy. • For women >65 years of age at risk for ischemic stroke or myocardial infarction, and in whom the concomitant risk of major bleeding is low, aspirin (75–100 mg/d) is suggested over no aspirin therapy.
National Institute for Health and Clinical Excellence (NICE): **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction[12] (2007)**	• Aspirin is recommended in all patients after a myocardial infarction and should be continued indefinitely. Clopidogrel should not be offered as first-line monotherapy after a myocardial infarction. • Clopidogrel combined with low-dose aspirin for 12 months is recommended in patients who have had a non-ST-segment-elevation acute coronary syndrome who are at moderate-to-high risk of myocardial infarction or death. Thereafter, patients may be treated with low-dose aspirin without clopidogrel in the absence of indication for dual antiplatelet therapy. • Patients who have been treated with aspirin and clopidogrel within the first 24 hours of an ST-segment-elevation myocardial infarction should continue on dual antiplatelet therapy for at least 4 weeks. Thereafter, low-dose aspirin should be continued and clopidogrel discontinued in the absence of indication for dual antiplatelet therapy. • If both clopidogrel and aspirin were not given during the acute phase of a myocardial infarction, this combination should not routinely be initiated. • Dual antiplatelet therapy with aspirin and clopidogrel should not be used for longer than 12 months after an acute myocardial infarction unless another indication for dual antiplatelet therapy exists. After an ST-segment-elevation myocardial infarction, the combination of aspirin and clopidogrel is usually recommended for a shorter duration than 12 months. • Clopidogrel monotherapy is an alternative treatment in patients with aspirin hypersensitivity. • Low-dose aspirin and a proton-pump inhibitor are recommended in patients with comorbid dyspepsia. A full-dose proton-pump inhibitor

Clinical Guideline	Recommendation(s)
	and low-dose aspirin should be considered in patients with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori.* • Patients being treated with warfarin for another indication should continue on warfarin. Those being treated with moderate-intensity warfarin (INR 2.0-3.0) and are at low risk of bleeding, may be treated with aspirin. The combination of warfarin and clopidogrel is not routinely recommended.
European Society of Cardiology (ESC): **Expert Consensus Document on the Use of Antiplatelet Agents[13] (2004)**	Major Recommendations for Individual Antiplatelet Agents • Aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. • Because of gastrointestinal toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting. • The available evidence supports daily doses of aspirin in the range of 75-100 mg for the long-term prevention of serious vascular events in high-risk patients (e.g., ≥3% per annum). • In clinical situations where an immediate antithrombotic effect is required (such as in acute coronary syndromes or in acute ischemic stroke), a loading dose of 160-300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of thromboxane A2-dependent platelet aggregation. • No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient. • The routine use of proton-pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75-100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting. • Nonsteroidal anti-inflammatory drugs have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin. • Because of potential pharmacodynamic interactions between traditional nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring nonsteroidal anti-inflammatory drug therapy may benefit from the use of selective COX-2 inhibitors. • The role of ticlopidine in the present therapeutic armamentarium is uncertain. • Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine. • In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent myocardial infarction. • Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has not been granted a claim of superiority versus aspirin by regulatory authorities. • Clopidogrel 75 mg daily is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin. • The results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial have led to Food and Drug Administration (FDA)

Clinical Guideline	Recommendation(s)
	approval of a new indication for clopidogrel in patients with acute coronary syndromes without ST-segment elevation. A loading dose of 300 mg clopidogrel should be used in this setting followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of percutaneous coronary intervention, length of clopidogrel treatment, and combination with GP IIb/IIIa antagonists. • Although the combination of low-dose aspirin and extended-release dipyridamole (200 mg twice a day) is considered an acceptable option for initial therapy of patients with non-cardioembolic cerebral ischemic events, there is no basis to recommend this combination in patients with ischemic heart disease.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina**[14] **(2007)**	• Aspirin should be started at 75-162 mg per day and continued indefinitely in all patients unless contraindicated. • The use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris**[15] **(2006)**	• Aspirin 75 mg daily is recommended in all patients without specific contraindications (e.g., active gastrointestinal bleeding, aspirin allergy or previous aspirin intolerance). Clopidogrel is an alternative antiplatelet agent in patients who cannot take aspirin. • The use of unopposed cyclooxygenase (COX)-2 inhibition is not recommended in patients with stable angina pectoris. • Clopidogrel may be combined with aspirin after coronary stenting or an acute coronary syndrome for a finite period of time, but combination therapy is currently not recommended for stable angina pectoris. • Dipyridamole is not recommended for antithrombotic treatment of stable angina.
American College of Chest Physicians (ACCP): **Antithrombotic Therapy in Atrial Fibrillation**[11] **(2008)**	• For patients with atrial fibrillation who have had a prior ischemic stroke, transient ischemic attack, or systemic embolism, long-term anticoagulation with an oral vitamin K antagonist (VKA) is recommended. • For patients with atrial fibrillation who are at intermediate risk of ischemic stroke and have one risk factor (age >75 years, history of hypertension, diabetes mellitus, and moderately or severely impaired left ventricular systolic function and/or heart failure), long-term antithrombotic therapy with an oral VKA or aspirin (75 to 325 mg/d) is recommended. Treatment with an oral VKA is given higher priority than aspirin. • For patients with atrial fibrillation <75 years of age with no risk factors, long-term aspirin therapy (75 to 325 mg/d) is recommended. • For patients with atrial flutter, the antithrombotic therapy decisions follow the same risk-based recommendations as for atrial fibrillation.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI) and Guidelines on**	<u>Initial and Hospital Management</u> • Oxygen, morphine, nitroglycerin, angiotensin-converting enzyme inhibitors, ß-blockers, and aspirin may be used in patients presenting with a myocardial infarction. Patients should be considered for reperfusion therapy. • Patients undergoing facilitated PCI may be treated with high dose aspirin, platelet GP IIb/IIIa inhibitors, and/or fibrinolytic therapy.

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Percutaneous Coronary Intervention (PCI)[16] (2009)	• Clopidogrel 75 mg/day should be initiated with aspirin and continued for 14 days regardless of whether reperfusion is performed. • In patients <75 years of age who receive fibrinolytic therapy or who do not receive reperfusion therapy, it is reasonable to administer an oral loading dose of clopidogrel 300 mg (no data are available to guide decision making regarding an oral loading dose in patients 75 years of age or older). • For primary PCI in STEMI, patients who receive prasugrel should receive a 60 mg loading dose. Prasugrel 10 mg daily may be used in addition to aspirin for chronic dual-antiplatelet therapy thereafter. • For secondary PCI in patients with recurrent ischemia or other reasons for planned PCI, 60 mg of prasugrel may be given after the coronary anatomy has been identified before, during, or within 1 hour of PCI. • In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days and preferably for 7 days unless the urgency for revascularization outweighs the risks of excess bleeding. • In patients taking prasugrel in whom CABG is planned, the drug should be withheld for at least 7 days prior to surgery. • Considerations of efficacy in the prevention of thrombosis and risk of an adverse event, particularly bleeding, should be considered when choosing a thienopyridine for PCI in STEMI. At this time, one product is not recommended over another. <u>Secondary Prevention</u> • Aspirin therapy is recommended for all patients post-PCI STEMI without aspirin resistance, allergy or increased risk of bleeding at a daily dose of 162-325 mg for at least 1 month after bare metal stent implantation, 3 months for sirolimus-eluting stent placement, and 6 months after paclitaxel-eluting stent placement. Thereafter, aspirin should be continued indefinitely at 75-162 mg daily. In patients at risk of bleeding, 75-162 mg daily aspirin is reasonable during the initial period after stent implantation. • Clopidogrel 75 mg daily should be given to all post-PCI patients who receive a drug-eluting stent for at least 12 months, and for a minimum of 1 month and ideally up to 12 months after placement of a bare metal stent (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). • Clopidogrel should be given for at least 14 days to patients not undergoing stent placement (medical therapy alone or PTCA without stenting). • Long-term therapy with clopidogrel 75 mg/day (e.g., 1 year) is reasonable in patients regardless of whether or not they receive reperfusion therapy. • Initiating and managing warfarin to an international normalized ratio (INR) of 2.0-3.0 is recommended in post-myocardial infarction patients with atrial fibrillation or flutter when clinically indicated. When therapy with aspirin, clopidogrel, and warfarin is indicated, an INR of 2.0-2.5 is recommended. <u>Comprehensive Risk Reduction for Patients With Coronary and Other Vascular Disease After PCI</u> • For all post-PCI stented patients without allergy or increased risk of bleeding, aspirin 162-325 mg daily should be given for at least 1 month after bare metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long-term aspirin use should be continued

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	indefinitely at a dose of 75-162 mg daily. • In patients for whom the physician is concerned about risk of bleeding, 75-162 mg of aspirin is reasonable during the initial period after stent implantation. • For all post-PCI patients who receive a drug-eluting stent, clopidogrel 75 mg daily should be given for at least 12 months (if the patient is not at high risk of bleeding). For post-PCI patients receiving a bare metal stent, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patients is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). • For all post-PCI non-stented STEMI patients, treatment with clopidogrel should continue for at least 14 days. • Long-term maintenance therapy (e.g., 1 year) with clopidogrel 75 mg QD is reasonable in STEMI and non-STEMI patients who undergo PCI without reperfusion therapy.
American College of Chest Physicians (ACCP): **Acute ST-Segment Elevation Myocardial Infarction (STEMI)**[22] **(2008)**	• For patients with acute ST-segment elevation myocardial infarction whether or not they receive fibrinolytic therapy, aspirin (160 to 325 mg) is recommended over no aspirin at the initial evaluation, followed by indefinite therapy (75 mg to 162 mg/d). • For patients with acute ST-segment elevation myocardial infarction, clopidogrel in addition to aspirin is recommended. The recommended dose of clopidogrel is 300 mg for patients <75 years of age and 75 mg for patients >75 years of age if they receive fibrinolytic agents or no reperfusion therapy, followed by 75 mg/d for up to 28 days. • For patients with acute ST-segment elevation myocardial infarction who have not received a coronary stent, clopidogrel 75 mg/d could be continued beyond 28 days and up to 1 year. • For patients undergoing primary PCI, clopidogrel in addition to aspirin is suggested at a dose of at least 300 mg, followed by 75 mg daily.
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-segment Elevation (STEMI)**[17] **(2008)**	Prophylactic Therapies in the Acute Phase • Aspirin 150-325 mg daily is recommended. • Aspirin should be started at a dose of 150–325 mg in a chewable form in all patients with a STEMI as soon as the diagnosis is confirmed. • Clopidogrel should be started as soon as possible in patients with a STEMI who undergo a PCI. Secondary Prevention • Aspirin 75-325 mg daily have been studied, but lower doses are effective with fewer side effects. Clopidogrel 75 mg daily may be used if aspirin is not tolerated. • Clopidogrel may be combined with aspirin for 3-12 months after an acute coronary artery syndrome without persistent ST-segment elevation. • The optimal duration of treatment length with clopidogrel after a STEMI has not been demonstrated.
American College of Chest Physicians (ACCP): **Antithrombotic Therapy for Non-ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)**[21] **(2008)**	• For all patients presenting with NSTE ACS, immediate aspirin (162 to 325 mg) and then daily oral aspirin (75 to 100 mg) is recommended. • For all NSTE ACS patients with an aspirin allergy, immediate treatment with clopidogrel, 300 mg bolus, followed by 75 mg/d is recommended indefinitely. • For NSTE ACS patients who are at moderate or greater risk for an ischemic event and who will undergo an early invasive management strategy, treatment with either clopidogrel (300 mg bolus, followed by 75 mg/d) or a GP IIb/IIIa inhibitor (eptifibatide or tirofiban) is recommended. • For NSTE ACS patients who are at moderate or greater risk for an

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	ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used, treatment with clopidogrel (300 mg bolus, followed by 75 mg/d) is recommended.
	• For NSTE ACS patients who undergo PCI, treatment with both clopidogrel and a GP IIb/IIIa inhibitor is recommended.
	  o A loading dose of 600 mg of clopidogrel should be given at least 2 hours prior to the PCI, followed by 75 mg/d.
	  o If ticlopidine is given, a loading dose of 500 mg should be given at least 6 hours prior to the planned PCI.
	  o For PCI patients who cannot tolerate aspirin, a loading dose of clopidogrel (600 mg) or ticlopidine (500 mg) should be given at least 24 hours prior to the planned PCI.
	  o The use of a GP IIb/IIIa antagonist is recommended for all NSTE ACS patients with at least moderate risk features undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream.
	• For NSTE ACS patients who have received clopidogrel and are scheduled for CABG, we suggest discontinuing clopidogrel for at least 5 days prior to the scheduled surgery (Grade 2A).

American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[18] (2007)**	<u>Early Hospital Care</u> • Aspirin should be administered as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication. • Clopidogrel should be administered to unstable angina (UA)/non–ST-elevation myocardial infarction (NSTEMI) patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. • In patients with a history of gastrointestinal bleeding, when aspirin and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly. • In patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel or an intravenous (IV) glycoprotein (GP) IIb/IIIa inhibitor. • In patients in whom an early initial conservative (e.g., noninvasive) strategy is selected, clopidogrel should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for at least 1 month and ideally up to 1 year. • In patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, heart failure, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed. Either an IV GP IIb/IIIa inhibitor or clopidogrel should be added to aspirin and anticoagulant therapy before diagnostic angiography (upstream). • For patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, or who undergo stress testing and are determined to be “low risk”, continue aspirin indefinitely. Continue clopidogrel for at least 1 month and ideally up to 1 year. • For patients in whom coronary artery bypass graft (CABG) surgery is selected, continue aspirin. Discontinue clopidogrel 5-7 days before elective CABG. • For patients in whom percutaneous coronary intervention (PCI) is selected, continue aspirin. Administer a loading dose of clopidogrel if

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	not started before diagnostic angiography. • For patients in whom medical therapy is selected after angiography and in whom no significant obstructive coronary artery disease (CAD) was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician. For patients in whom evidence of coronary atherosclerosis is present (albeit without flow-limiting stenoses), long-term treatment with aspirin and other secondary prevention measures should be prescribed. • For patients in whom medical therapy is selected after angiography and in whom CAD was found on angiography, continue aspirin. Administer a loading dose of clopidogrel if not given before diagnostic angiography. • For patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, continue aspirin indefinitely. Continue clopidogrel for at least 1 month and ideally up to 1 year. <u>Long-Term Medical Therapy and Secondary Prevention</u> • For patients treated medically without stenting, aspirin (75-162 mg per day) should be prescribed indefinitely. Clopidogrel (75 mg per day) should be prescribed for at least 1 month and ideally for up to 1 year. For aspirin-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization. For clopidogrel-allergic patients, use ticlopidine (250 mg twice daily). • For UA/NSTEMI patients treated with bare-metal stents, aspirin 162-325 mg per day should be prescribed for at least 1 month, and then continued indefinitely at a dose of 75-162 mg per day. Clopidogrel should be prescribed at a dose of 75 mg per day for a minimum of 1 month and ideally for up to 1 year (unless the patient is at increased risk of bleeding, then it should be given for a minimum of 2 weeks). • For UA/NSTEMI patients treated with drug-eluting stents (DES), aspirin 162-325 mg per day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation then continued indefinitely at a dose of 75-162 mg per day. Clopidogrel 75 mg daily should be given for at least 12 months to all post-PCI patients receiving DES. • Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as proton-pump inhibitors).
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE-ACS)[19] (2007)**	• Aspirin is recommended for all patients presenting with NSTE ACS without contraindication at an initial loading dose of 160-325 mg (non-enteric), and at a maintenance dose of 75-100 mg long term. • For all patients, an immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily. Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding. • For all patients with contraindication to aspirin, clopidogrel should be given instead. • In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function. • In patients pretreated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible. • Nonsteroidal anti-inflammatory agents should not be administered with

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	aspirin or clopidogrel. • Interruption of dual antiplatelet therapy with aspirin and clopidogrel during the first 12 months after the initial event is not recommended unless severe, life-threatening bleeding occurs, or surgery is to be performed during which minor bleeding may result in serious consequences.
American College of Chest Physicians (ACCP): **Antithrombotic Therapy for Peripheral Artery Occlusive Disease**[20] **(2008)**	• In peripheral artery occlusive disease patients with clinically manifest coronary or cerebrovascular disease, lifelong antiplatelet therapy is recommended in comparison to no antiplatelet therapy. • In those without clinically manifest coronary or cerebrovascular disease, aspirin (75–100 mg/d) is recommended over clopidogrel. • In patients who are aspirin intolerant, we recommend clopidogrel over ticlopidine. • For patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention, cilostazol is recommended. Clinicians should not use cilostazol in those with less disabling claudication. The use of pentoxifylline is not recommended. • In patients undergoing carotid endarterectomy, aspirin (75–100 mg) is recommended preoperatively to prevent perioperative ischemic neurologic events. Lifelong postoperative aspirin (75–100 mg/d) is recommended. • In nonoperative patients with asymptomatic carotid stenosis (primary or recurrent), lifelong aspirin (75–100 mg/d) is recommended. Dual antiplatelet therapy with aspirin and clopidogrel is not recommended. • For patients undergoing lower-extremity balloon angioplasty (with or without stenting), long-term aspirin (75–100 mg/d) is recommended.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients With Peripheral Arterial Disease**[26] **(2005)**	<u>Antiplatelet and Antithrombotic Drugs</u> • Antiplatelet therapy is indicated to reduce the risk of myocardial infarction, stroke, or vascular death in individuals with atherosclerotic lower extremity peripheral arterial disease. • Aspirin 75-325 mg/day is recommended as safe and effective antiplatelet therapy. • Clopidogrel 75 mg/day is recommended as an effective alternative antiplatelet therapy. • Warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity peripheral arterial disease. <u>Claudication</u> • Cilostazol 100 mg twice daily is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity peripheral arterial disease and intermittent claudication (in the absence of heart failure). • A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure).
National Institute for Health and Clinical Excellence (NICE): **Clopidogrel and Modified-release Dipyridamole in the Prevention of Occlusive Vascular Events**[25] **(2005)**	• This guidance applies to people who have had an occlusive vascular event, or who have symptomatic peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with atrial fibrillation, or who require treatment to prevent occlusive events after coronary revascularization or carotid artery procedures. • The combination of modified-release (MR) dipyridamole and aspirin is recommended for people who have had an ischemic stroke or a transient ischemic attack for a period of 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative

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	therapy should revert to standard care (including long-term treatment with low-dose aspirin). • Clopidogrel alone (within its licensed indications) is recommended for people who are intolerant of low-dose aspirin and either have experienced an occlusive vascular event or have symptomatic peripheral arterial disease. Aspirin intolerance is defined as either a proven hypersensitivity to aspirin-containing medicines or history of severe dyspepsia induced by low-dose aspirin. • Clopidogrel is licensed in the United Kingdom (UK) for the prevention of atherothrombotic events in people who have had a myocardial infarction (from a few days until less than 35 days), have had an ischemic stroke (from 7 days until less than 6 months), or have established peripheral arterial disease. MR dipyridamole is licensed in the UK for the secondary prevention of ischemic stroke and TIAs, either alone or in combination with aspirin. (MR dipyridamole is not available without aspirin in the United States.)
American Heart Association (AHA)/American Stroke Association (ASA): **Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack[23] (2008)**	Antithrombotic Therapy for Non-cardioembolic Stroke or Transient Ischemic Attack (TIA) • For patients with non-cardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulants are recommended to reduce the risk of recurrent stroke and other cardiovascular events. Aspirin (50 to 325 mg/day), the combination of aspirin and extended-release (ER) dipyridamole, and clopidogrel are all acceptable options for initial therapy. • Compared with aspirin alone, both the combination of aspirin and ER dipyridamole and clopidogrel are safe. The combination of aspirin and ER dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone on the basis of direct-comparison trials. Insufficient data are available to make evidence-based recommendations about choices between antiplatelet options other than aspirin. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, tolerance, and other clinical characteristics. • The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients. • For patients allergic to aspirin, clopidogrel is reasonable. • For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered for non-cardioembolic patients, no single agent or combination has been studied in patients who have had an event while receiving aspirin.
American College of Chest Physicians (ACCP): **Antithrombotic and Thrombolytic Therapy for Ischemic Stroke[24] (2008)**	• For patients with acute ischemic stroke who are not receiving thrombolysis, early aspirin therapy is recommended. • For patients who have experienced a non-cardioembolic stroke or transient ischemic attack, treatment with an antiplatelet drug is recommended. Aspirin, the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy. • For patients who have experienced a non-cardioembolic stroke or transient ischemic attack, the combination of aspirin and extended-release dipyridamole is recommended over aspirin; clopidogrel is suggested over aspirin. • For most patients with a non-cardioembolic stroke or transient ischemic attack, the long-term use of the combination of aspirin and clopidogrel should be avoided. In those with a recent acute myocardial

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	infarction, other acute coronary syndrome, or a recently placed coronary stent, clopidogrel plus aspirin is recommended. The optimal duration of dual antiplatelet therapy depends on the specific cardiac indication. • For patients who are allergic to aspirin, clopidogrel is recommended. • For patients with a non-cardioembolic stroke or transient ischemic attack, antiplatelet agents are recommended over oral anticoagulation • For patients undergoing carotid endarterectomy, aspirin (50 to 100 mg/d) is recommended prior to and following the procedure. • For patients with atrial fibrillation who have suffered a recent stroke or transient ischemic attack, long-term oral anticoagulation is recommended. • For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, aspirin at a dose of 75–325 mg/d is recommended. • For patients with stroke associated with aortic atherosclerotic lesions, antiplatelet therapy is recommended over no therapy. • For patients with cryptogenic stroke associated with mobile aortic arch thrombi, either oral anticoagulation or antiplatelet agents are recommended. • For patients with cryptogenic ischemic stroke and a patent foramen ovale, antiplatelet therapy is recommended over no therapy; antiplatelet agents are suggested over anticoagulation. • For patients with mitral valve strands or prolapse, who have a history of transient ischemic attack or stroke, antiplatelet therapy is recommended.
American College of Chest Physicians (ACCP): **Valvular and Structural Heart Disease[27] (2008)**	• For patients with rheumatic mitral valve disease complicated by the presence of atrial fibrillation, previous systemic embolism, and/or left atrial thrombus, oral VKA therapy is recommended. • For patients with rheumatic mitral valve disease with atrial fibrillation who suffer systemic embolism or have left atrial thrombus while receiving VKAs at a therapeutic INR, the addition of low-dose aspirin therapy (50 to 100 mg/d) is recommended after consideration of the additional hemorrhagic risks. • For patients with mitral valve prolapse (MVP) who have documented transient ischemic attacks or ischemic stroke, long-term aspirin therapy (50 to 100 mg/d) is recommended. • For patients with mitral annular calcification complicated by systemic embolism, ischemic stroke, or transient ischemic attack, who do not have atrial fibrillation, aspirin therapy (50 to 100 mg/d) is recommended. • For patients with isolated calcific aortic valve disease who have experienced ischemic stroke or transient ischemic attack not attributable to another source, aspirin therapy (50 to 100 mg/d) is recommended. • For patients with ischemic stroke associated with aortic atherosclerotic lesions, aspirin therapy (50 to 100 mg/d) is recommended over no therapy. • For patients with ischemic stroke associated with mobile aortic arch thrombi, treatment with either an oral VKA or aspirin (50 to 100 mg/d) is recommended. • For patients with mechanical heart valves who have additional risk factors for thromboembolism, such as atrial fibrillation, hypercoagulable state, or low ejection fraction, or who have a history of atherosclerotic vascular disease, aspirin therapy (50 to 100 mg/d)

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	should be added to long-term VKA therapy. Aspirin should not be added to VKA therapy in patients with mechanical heart valves who are at particularly high risk of bleeding (history of GI bleed or age>80 years). • For patients with mechanical prosthetic heart valves who suffer systemic embolism despite a therapeutic INR, the addition of aspirin therapy (50 to 100 mg/d) is recommended and/or upward titration of VKA therapy to achieve a higher target INR. • For patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, aspirin therapy (50 to 100 mg/d) is recommended. • For patients with bioprosthetic valves who have additional risk factors for thromboembolism, including atrial fibrillation, hypercoagulable state, or low ejection fraction, VKA therapy is recommended. The addition of aspirin (50 to 100 mg/d) may be considered, especially in patients with a history of atherosclerotic vascular disease. Aspirin should not be added to long-term VKA therapy patients with bioprosthetic heart valves who are at high risk of bleeding (history of GI bleed or age>80 years).

III. Indications

The Food and Drug Administration (FDA)-approved indications for the platelet-aggregation 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 Platelet-Aggregation Inhibitors[1-9]

Indication	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Acute Coronary Syndromes							
Reduce the rate of a combined end point of cardiovascular death, myocardial infarction, or stroke, as well as the rate of a combined end point of cardiovascular death, myocardial infarction, stroke, or refractory ischemia in patients with non–ST-segment elevation acute coronary syndrome (unstable angina /non–ST-elevation myocardial infarction [NSTEMI]), including patients who are to be managed medically and those who are to be managed with coronary revascularization				✔			
Reduce the rate of death from any cause and the rate of a combined end point of death, reinfarction, or stroke in patients with ST-elevation myocardial infarction (STEMI)				✔ †			
Reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows: patients with unstable angina or non–ST elevation MI (NSTEMI); patients with ST elevation MI (STEMI) when managed with primary or delayed PCI						✔	
Atherothrombotic/Vascular Events							
Reduce the combined risk of death and nonfatal myocardial infarction in patients with a previous myocardial infarction or unstable angina pectoris	✔						
Reduce the combined risk of myocardial infarction and sudden death in patients with chronic stable angina pectoris	✔						
Reduce the risk of vascular mortality in patients with a suspected acute myocardial infarction	✔						
Reduce the rate of a combined end point of new ischemic stroke (fatal or not), new myocardial infarction (fatal or				✔			

Indication	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
not), and other vascular death in patients with a history of recent myocardial infarction, recent stroke, or established peripheral arterial disease							
Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation as adjunctive therapy with aspirin							✔
Reduce postoperative thromboembolic complications of cardiac valve replacement as an adjunct to coumarin anticoagulants					✔		
Intermittent Claudication							
For the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance			✔				
Ischemic Stroke or Transient Ischemic Attack							
Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli	✔						
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis		✔					
Reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke							✔ *
Miscellaneous Indications							
Fever	✔						
Generalized aches and pains	✔						
Headache	✔						
Relief of signs and symptoms of rheumatic diseases	✔						

*Because ticlopidine is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia, agranulocytosis and aplastic anemia, it should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.
†The benefit of clopidogrel for patients who undergo primary percutaneous coronary intervention is unknown.

IV. Pharmacokinetics

The pharmacokinetic parameters of the platelet-aggregation inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Platelet-Aggregation Inhibitors[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aspirin	50-75	50-80	Liver	Renal (6-36)	3-10
Cilostazol	87-100	95-98	Liver	Renal (74) Feces (20)	11-13
Clopidogrel	50	94-98	Liver	Renal (50) Feces (46)	6-8
Dipyridamole	37-66	91-99	Liver	Feces	10-12
Prasugrel	79	98	Liver	Renal (68-70) Feces (25-27)	7-8
Ticlopidine	80-90	98	Liver	Renal (60) Feces (23)	13

V. Drug Interactions

Significant drug interactions with the platelet-aggregation inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Platelet-Aggregation Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Aspirin	1	Clopidogrel	Concurrent therapy may increase the risk of life-threatening bleeding (e.g., intracranial and gastrointestinal hemorrhage) in high-risk patients with transient ischemic attack or ischemic stroke. Avoid aspirin use in high-risk patients with recent ischemic stroke or transient ischemic attack who are receiving clopidogrel.
Aspirin	1	Heparin	Aspirin can inhibit platelet aggregation and has caused bleeding. The risk of bleeding may be increased when aspirin and heparin are used together. Monitor coagulation parameters and signs of bleeding if the combination is used.
Aspirin	1	Influenza Virus Vaccine, Intranasal	Intranasal influenza virus vaccine is contraindicated in children and adolescents on aspirin therapy as the risk of Reye syndrome may be increased.
Aspirin	1	Ketorolac	Aspirin may displace ketorolac from protein binding sites and have synergistic side effects. Ketorolac is contraindicated in patients receiving aspirin due to an increased risk of serious ketorolac-related side effects.
Aspirin	1	Methotrexate	Salicylates may increase the toxic effects of methotrexate by decreasing methotrexate's renal clearance and

Generic Name(s)	Significance Level	Interaction	Mechanism
			plasma protein binding. When salicylates are coadministered, the dose of methotrexate may need to be decreased or prolonged regimens of leucovorin rescue may be indicated. Dosage adjustment may also be guided by monitoring methotrexate plasma levels.
Aspirin	1	Nonsteroidal anti-inflammatory drugs (NSAIDs)	The pharmacologic effects of some NSAIDs may be decreased and the cardioprotective effect of low-dose uncoated aspirin may be reduced with concurrent administration of NSAIDs and aspirin. Both aspirin and NSAIDs are also gastric irritants. Consider using analgesics that do not interfere with antiplatelet effect (e.g., acetaminophen).
Aspirin	1	Warfarin	The anticoagulant activity of warfarin and the risk of hemorrhage may be enhanced by the effects of aspirin on the gastric mucosa and platelet function. If concurrent use cannot be avoided, frequently monitor the patient's international normalized ratio (INR) and adjust the warfarin dose accordingly, especially when starting or stopping aspirin therapy.
Clopidogrel	1	Proton-pump Inhibitors	Proton pump inhibitors interfere with the metabolic conversion of clopidogrel at CYP2C19 to its active metabolite, thus decreasing the antiplatelet activity of clopidogrel.
Aspirin	2	Angiotensin-converting enzyme (ACE) inhibitors	Aspirin inhibits prostaglandin synthesis and may reduce the hypotensive and vasodilator effects of the ACE inhibitor. Monitor blood pressure and hemodynamic parameters if both agents are needed.
Aspirin	2	β-blockers	Salicylates may inhibit the synthesis of prostaglandins involved in the antihypertensive activity of β-blockers; therefore, the blood pressure-lowering effects of β-blockers may be reduced. In addition, the beneficial effects of β-blockers on left ventricular ejection fraction in patients with chronic heart failure may be attenuated; however, the mechanism of this interaction is not known.
Aspirin	2	Carbonic anhydrase inhibitors	Concurrent administration of carbonic anhydrase inhibitors and salicylates may result in the accumulation of carbonic anhydrase

Generic Name(s)	Significance Level	Interaction	Mechanism
			inhibitors and toxicity (e.g., central nervous system depression, metabolic acidosis). Aspirin displaces carbonic anhydrase inhibitors from plasma protein binding sites and inhibits renal clearance. Metabolic acidosis may lead to increased penetration of salicylates into the central nervous system. Minimize or avoid coadministration of salicylates and carbonic anhydrase inhibitors.
Aspirin	2	Corticosteroids	Corticosteroids may reduce serum salicylate levels by stimulating liver metabolism of salicylates and increasing renal elimination. The effectiveness of salicylates may be decreased. When adding or withdrawing corticosteroids, tailor the salicylate dosage and monitor plasma salicylate concentrations.
Aspirin	2	Insulin	Salicylates may potentiate the serum glucose-lowering action of insulin by increasing basal insulin concentrations and enhancing the acute insulin response to a glucose load. Blood glucose levels should be monitored and insulin regimens tailored as needed.
Aspirin	2	Probenecid	Coadministration of probenecid and aspirin may inhibit the uricosuric action of either drug alone. The mechanism of this interaction is not known but may be due to an alteration in the renal filtration of uric acid. Coadministration should be avoided to allow maximum uricosuria to be attained. Aspirin therapy dosed at non-antiinflammatory concentrations may be acceptable in patients who require both agents.
Aspirin	2	Sulfinpyrazone	Salicylates may displace sulfinpyrazone from plasma protein binding sites and may block the inhibitory effects of sulfinpyrazone on tubular reabsorption of uric acid. Patients should be counseled not to take salicylate-containing products on a regular or extended basis since the uricosuria produced by sulfinpyrazone may be suppressed.
Aspirin	2	Sulfonylureas	Salicylates may increase the hypoglycemic effect of sulfonylureas by several mechanisms. Salicylates reduce basal plasma glucose levels,

Generic Name(s)	Significance Level	Interaction	Mechanism
			enhance insulin secretion and inhibit acute insulin responses to glucose. Salicylates may also displace sulfonylureas from protein binding sites. Monitor the patient's blood glucose and if hypoglycemia develops, consider decreasing the sulfonylurea dose. Consider alternative therapy with acetaminophen or an NSAID.
Aspirin	2	Valproic acid	Aspirin may displace valproic acid from protein binding sites and increase the free fraction of valproic acid, leading to toxic effects. Aspirin may also alter the metabolic pathways of valproic acid. Monitor serum valproic acid concentrations (including free fraction if readily available), symptoms of valproic acid toxicity and liver enzymes when aspirin is coadministered with valproic acid.
Cilostazol	2	Clarithromycin, erythromycin	Certain macrolide antibiotics may inhibit the metabolism (CYP3A4) of cilostazol leading to increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects. Consider decreasing the dose of cilostazol during coadministration with certain macrolide antibiotics.
Cilostazol	2	Omeprazole	Omeprazole may inhibit the metabolism (CYP2C19) of cilostazol leading to increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects. Consider decreasing the dose of cilostazol during coadministration of omeprazole.
Clopidogrel	2	Ketoconazole	Ketoconazole may inhibit the isozymes (CYP3A4 and CYP3A5) that convert the prodrug clopidogrel to its active metabolite. If possible, avoid coadministration of these agents since the antiplatelet effect of clopidogrel may be inhibited.
Dipyridamole	2	Adenosine	Dipyridamole may potentiate the pharmacologic effects of adenosine by inhibiting the transport or metabolism of adenosine. Following rapid bolus administration of adenosine, profound bradycardia may occur.
Ticlopidine	2	Cyclosporine	Through an unknown mechanism, ticlopidine decreases cyclosporine whole blood concentrations and

Generic Name(s)	Significance Level	Interaction	Mechanism
			pharmacologic effects. If ticlopidine therapy is started or discontinued, consider frequent monitoring of cyclosporine blood concentrations. Adjust the dose of cyclosporine or discontinue ticlopidine as indicated.
Ticlopidine	2	Hydantoins	Ticlopidine may inhibit hydantoin metabolism thereby increasing plasma hydantoin concentrations and adverse effects. Monitor hydantoin levels and make dosage adjustments as needed. Also, observe the patient's clinical response when starting, stopping, or changing the dose of ticlopidine.
Ticlopidine	2	Theophyllines	Ticlopidine may impair theophylline elimination. Theophylline levels may increase and lead to toxicity (e.g., nausea, vomiting, seizures and arrhythmias). Monitor theophylline serum levels when ticlopidine is added or withdrawn from a patient's regimen and tailor dosages 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 platelet-aggregation inhibitors are listed in Table 6. The boxed warnings for the platelet-aggregation inhibitors are listed in Tables 7 – 10.

Table 6. Adverse Drug Events (%) Reported with the Platelet-Aggregation Inhibitors[1-9]

Adverse Events	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Cardiovascular							
Angina pectoris	-	<1	-	-	✔	-	-
Arrhythmia	-	<1	-	-	-	-	-
Atrial fibrillation/flutter	✔	-	<2	1-3	-	3	-
Bradycardia	-	-	-	-	-	3	-
Cardiac arrest	-	-	<2	-	-	-	-
Cardiac failure	-	2	-	1-3	-	-	-
Chest pain	-	-	-	8	-	3	-
Conduction defect	✔	-	-	-	-	-	-
Congestive heart failure	-	-	<2	-	-	-	-
Coronary artery spasm	✔	-	-	-	-	-	-
Dysrhythmias	✔	-	-	-	-	-	-
Edema	✔	-	-	4	-	3	-
Hypertension	-	-	-	4	-	8	-
Hypotension	✔	-	<2	-	✔	4	-
Myocardial infarction/ischemia	-	-	<2	-	-	-	-
Nodal arrhythmia	-	-	<2	1-3	-	-	-
Palpitation	-	-	5-10	-	✔	-	-
Peripheral edema	-	-	7-9	-	-	-	-
Postural hypotension	-	-	<2	-	-	-	-
QTc prolongation	-	-	<2	-	-	-	-
Supraventricular tachycardia	-	-	<2	-	-	-	-
Syncope	-	1	<2	1-3	-	-	-
Tachycardia	✔	-	4	-	✔	-	-
Torsades de pointes	-	-	<2	-	-	-	-
Ventricular tachycardia	-	-	<2	-	-	-	-
Central Nervous System							
Agitation	✔	-	-	-	-	-	-
Amnesia	-	2	-	-	-	-	-
Anxiety	-	-	-	1-3	-	-	-
Cerebral edema	✔	<1	-	-	-	-	-

Adverse Events	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Cerebral hemorrhage	-	<1	-	<1	-	-	<1
Cerebral infarction/ischemia	-	-	<2	-	-	-	-
Coma	✔	<1	-	-	-	-	-
Confusion	✔	1	-	<1	-	-	-
Delirium	✔	-	-	-	-	-	-
Depression	-	-	-	4	-	-	-
Dizziness	✔	-	9-10	2-6	14	4	-
Extremity pain	-	-	-	-	-	3	-
Fatigue	✔	6	-	3	-	4	-
Fever	-	-	-	1-3	-	5	-
Flushing	-	-	-	-	✔		-
Hallucination	-	-	<1	-	-		-
Headache	✔	38	27-34	3-8	2	2	-
Hyperthermia	✔	-	-	-	-	-	-
Insomnia	✔	-	-	1-3	-	-	-
Ischemic brain infarction	✔	-	-	-	-	-	-
Lethargy/malaise	✔	2	-	-	✔	-	-
Nervousness	✔	-	-	-	-	-	-
Pain	-	6	-	6	-	-	-
Seizure	-	2	-	-	-	-	-
Somnolence	-	1	-	-	-	-	-
Subdural hematoma	-	-	<2	-	-	-	-
Vertigo	-	-	<3	1-3	-	-	-
Dermatologic							
Alopecia	-	<1	-	-	✔	-	-
Angioedema	✔	-	-	-	-	-	-
Bullous eruption	-	-	-	<1	-	-	-
Eczema	-	-	-	1-3	-	-	-
Erythema multiforme	-	-	-	<1	-	-	<1
Erythema nodosum	-	-	-	-	-	-	<1
Exfoliative dermatitis	-	-	-	-	-	-	<1
Extradural hematoma	-	-	<2	-	-	-	-
Ischemic necrosis	-	-	-	<1	-	-	-
Lichen planus	-	-	-	<1	-	-	-
Maculopapular rash	-	-	-	<1	-	-	<1
Purpura	-	1	-	-	-	-	2
Pruritus	-	<1	-	3	✔	-	1

Adverse Events	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Rash	✔	<1	-	4	2	3	5
Stevens-Johnson syndrome	-	-	<2	-	-	-	<1
Toxic epidermal necrolysis	-	-	-	<1	-	-	-
Ulceration	-	<1	-	-	-	-	-
Urticaria	✔	<1	-	<1	-	-	<1
Endocrine and Metabolic							
Acidosis	✔	-	-	-	-	-	-
Dehydration	✔	-	-	-	-	-	-
Diabetes mellitus	-	-	<2	-	-	-	-
Gout/hyperuricemia	-	-	<2	1-3	-	-	-
Hypercholesterolemia	-	-	4	-	-	7	>10
Hyperglycemia	✔	-	-	-	-	-	-
Hyperkalemia	✔	-	-	-	-	-	-
Hypoglycemia	✔	-	-	-	-	-	-
Hyponatremia	✔	-	-	-	-	-	<1
Pancreatitis	-	<1	-	<1	-	-	-
Gastrointestinal							
Abdominal distress	-	-	-	-	6	-	-
Abdominal pain	✔	18	4-5	2-6	-	-	4
Abnormal stools	-	-	12-15	-	-	-	1
Anorexia	-	1	-	-	-	-	-
Bleeding	-	4	-	-	-	-	-
Chronic diarrhea	-	-	-	-	-	-	<1
Colitis	✔	-	<2	-	-	-	-
Colonic ulceration	✔	-	-	-	-	-	-
Constipation	-	-	-	1-3	-	-	-
Diarrhea	-	13	12-19	2-5	✔	-	13
Duodenal ulcer	✔	-	<2	-	-	2	-
Duodenitis	-	-	<2	-	-	-	-
Dyspepsia	✔	>10	6	2-5	✔	-	7
Epigastric discomfort/heartburn	✔	-	-	-	-	-	-
Esophageal hemorrhage	-	-	<2	-	-	-	-
Esophageal stricture	✔	-	-	-	-	-	-
Esophageal ulcer	✔	-	-	-	-	-	-
Esophagitis	✔	-	<2	-	-	-	-
Flatulence	-	-	2-3	-	-	-	2
Gastric erosions	✔	-	-	-	-	-	-

Adverse Events	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Gastric erythema	✔	-	-	-	-	-	-
Gastrointestinal hemorrhage	-	1	-	1-3	-	2	<1
Hematemesis	-	<1	-	-	-	-	-
Hemorrhoids	-	1	-	-	-	-	-
Nausea	✔	16	6-7	3	✔	5	7
Oral mucosal ulcers	✔	-	-	-	-	-	-
Peptic ulcer	6-31	-	<2	-	-	-	<1
Periodontal abscess	-	-	<2	-	-	-	-
Rectal bleeding	-	2	<2	-	-	-	-
Rectal stenosis	✔	-	-	-	-	-	-
Retroperitoneal hemorrhage	-	-	<2	<1	-	-	-
Vomiting	✔	8	-	1-3	✔	-	2
Genitourinary						-	
Blood urea nitrogen increased	✔	-	-	-	-	-	-
Cystitis	-	-	<2	1-3	-	-	-
Hematuria	-	-	-	<1	-	-	<1
Interstitial nephritis	✔	<1	-	-	-	-	-
Menorrhagia	-	-	-	-	-	-	<1
Papillary necrosis	✔	<1	-	-	-	-	-
Proteinuria	✔	-	-	-	-	-	-
Renal failure	✔	<1	-	-	-	-	<1
Serum creatinine increased	✔	-	-	-	-	-	<1
Urinary tract infection	-	-	-	3	-	-	-
Uterine hemorrhage	-	<1	-	-	-	-	-
Hematologic							
Agranulocytosis	-	-	<2	<1	-	-	<1
Anemia	✔	2	<2	1-3	-	2	-
Aplastic anemia	-	<1	-	<1	-	-	<1
Bleeding	✔	-	-	4-5	-	-	-
Coagulopathy	✔	-	-	-	-	-	-
Disseminated intravascular coagulation	✔	<1	-	-	-	-	-
Eosinophilia	-	-	-	-	-	-	<1
Epistaxis	-	-	-	3	-	-	-
Granulocytopenia	-	-	<2	<1	-	-	-
Hematoma	-	-	-	1-3	-	✔	-
Hemolytic anemia	✔	-	-	-	-	-	<1
Hemorrhage	-	-	<2	-	-	✔	-

Adverse Events	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Hypochromic anemia	-	-	-	<1	-	-	-
Iron deficiency anemia	✔	-	-	-	-	-	-
Leukopenia	-	-	<2	<1	-	3	-
Neutropenia	-	-	-	<1	-	-	2
Pancytopenia	-	<1	-	<1	-	-	<1
Polycythemia	-	-	<2	-	-	-	-
Prothrombin time prolonged	✔	<1	-	-	-	-	-
Purpura	-	-	-	5	-	-	-
Thrombocytopenia	✔	<1	<2	<1	✔	✔	<1
Thrombocytosis	-	-	-	-	-	-	<1
Thrombosis	-	-	<2	-	-	-	-
Thrombotic thrombocytopenic purpura	-	-	-	-	-	-	<1
Hepatic							
Acute liver failure	-	-	-	<1	-	-	-
Bilirubinemia	-	-	-	<1	-	-	-
Cholelithiasis	-	<1	<2	-	✔	-	-
Fatty liver	-	-	-	<1	-	-	-
Hepatic dysfunction	-	-	<2	-	-	✔	-
Hepatic failure	-	<1	-	-	-	-	-
Hepatic necrosis	-	-	-	-	-	-	<1
Hepatitis	✔	<1	-	<1	✔	-	<1
Hepatotoxicity	✔	-	-	-	-	-	-
Jaundice	✔	<1	-	-	-	-	<1
Liver dysfunction	-	-	-	-	✔	-	-
Liver function test abnormalities	-	-	-	<3	-	-	1
Transaminases increased	✔	-	-	-	-	-	-
Musculoskeletal							
Acetabular bone destruction	✔	-	-	-	-	-	-
Arthralgia	-	6	-	6	-	-	-
Arthritis	-	2	-	1-3	✔	-	-
Arthropathy	-	-	-	-	-	-	<1
Arthrosis	-	1	-	-	-	-	-
Back pain	-	5	6-7	6	-	5	-
Bursitis	-	-	<2	-	-	-	-
Fatigue	-	-	-	-	✔	-	-
Leg cramps	-	-	-	1-3	-	-	-
Myalgia	-	1	2-3	-	✔	-	-

Adverse Events	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Myositis	-	-	-	-	-	-	<1
Neuralgia	-	-	<2	1-3	-	-	-
Paresthesia	-	<1	-	1-3	✔	-	-
Peripheral neuropathy	-	-	-	-	-	-	<1
Rhabdomyolysis	✔	<1	-	-	-	-	-
Weakness	✔	2	-	1-3	-	-	-
Respiratory							
Asthma	✔	-	<2	-	-	-	-
Bronchiolitis obliterans	-	-	-	-	-	-	<1
Bronchitis	-	-	-	4	-	-	-
Bronchospasm	✔	<1	-	-	-	-	-
Cough	-	2	3-4	3	-	4	-
Dyspnea	✔	<1	-	5	-	5	-
Epistaxis	-	2	-	-	-	6	-
Hemoptysis	-	<1	-	<1	-	-	-
Hemothorax	-	-	-	<1	-	-	-
Hyperpnea	✔	-	-	-	-	-	-
Intestinal pneumonitis	-	-	-	<1	-	-	-
Larynx edema	✔	-	-	-	✔	-	-
Pharyngitis	-	-	7-10	-	-	-	-
Pneumonia	-	-	<2	-	-	-	-
Pneumonitis	-	-	-	-	-	-	<1
Pulmonary edema	✔	<1	-	-	-	-	-
Pulmonary hemorrhage	-	-	-	<1	-	-	-
Respiratory alkalosis	✔	-	-	-	-	-	-
Rhinitis	-	-	7-12	4	-	-	-
Rhinosinusitis	✔	-	-	-	-	-	-
Tachypnea	✔	<1	-	-	-	-	-
Upper respiratory infection	-	1	-	-	-	-	-
Other							
Allergic reaction	-	<1	-	<1	-	✔	-
Allergic vasculitis	-	<1	-	-	-	-	-
Anaphylactoid reaction/anaphylaxis	-	<1	-	<1	-	-	<1
Angioedema	-	<1	-	<1	-	✔	<1
Ante-/peri-/postpartum bleeding	✔	<1	-	-	-	-	-
Blindness	-	-	<2	-	-	-	-
Cataract	-	-	-	1-3	-	-	-

Adverse Events	Aspirin	Aspirin/ Dipyridamole	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticlopidine
Conjunctival bleeding	-	-	-	-	-	-	<1
Conjunctivitis	-	-	-	1-3	-	-	-
Deafness	-	<1	-	-	-	-	-
Fever	-	-	-	<1	-	-	-
Flu symptoms	-	-	-	8	-	-	-
Hearing loss	✔	-	-	-	-	-	-
Hypersensitivity reaction	-	-	-	<1	✔	-	-
Infection	-	-	10-14	-	-	-	-
Lower weight infants	✔	<1	-	-	-	-	-
Ocular/retinal hemorrhage	-	-	<2	<1	-	-	-
Periorbital edema	✔	-	-	-	-	-	-
Positive antinuclear antibody	-	-	-	-	-	-	<1
Prolonged pregnancy and labor	✔	-	-	-	-	-	-
Reye's syndrome	✔	<1	-	-	-	-	-
Sepsis	-	-	-	-	-	-	<1
Serum sickness	-	-	-	<1	-	-	<1
Stillbirths	✔	<1	-	-	-	-	-
Systemic lupus erythematosus	-	-	-	-	-	-	<1
Taste disorder	-	-	-	<1	-	-	-
Tinnitus	✔	-	-	-	-	-	-
Vasculitis	-	-	-	<1	-	-	<1

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Cilostazol[1]

WARNING
Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity.

Table 8. Boxed Warning for Clopidogrel[1]

WARNING
The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 system, primarily CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used an as aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Table 9. Boxed Warning for Prasugrel[1]

WARNING
Prasugrel can cause significant, sometimes fatal, bleeding. Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack (TIA) or stroke. In patients 75 years of age and older, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior myocardial infarction [MI]) in which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue prasugrel at least 7 days prior to any surgery. Additional risk factors for bleeding include body weight less than 60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDs]). Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of prasugrel. If possible, manage bleeding without discontinuing prasugrel. Discontinuing prasugrel, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular (CV) events.

Table 10. Boxed Warning for Ticlopidine[1]

WARNING
Ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura (TTP) and aplastic anemia. Neutropenia/Agranulocytosis: Among 2,048 patients in clinical trials in stroke patients, there were 50 cases (2.4%) of neutropenia (less than 1,200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of these patients (0.8% of the total population). TTP: One case of thrombotic thrombocytopenic purpura was reported during clinical trials in stroke patients. Based on postmarketing data, United States (US) physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated TTP may be as high as one case in every 2,000 to 4,000 patients exposed. Aplastic Anemia: Aplastic anemia was not seen during clinical trials in stroke patients, but US physicians reported about 50 cases between 1992 and 1998. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated aplastic anemia may be as high as one case in every 4,000 to 8,000 patients exposed. Monitoring of Clinical and Hematologic Status: Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks. The incidence of aplastic anemia peaks after about 4 to 8 weeks of therapy. The incidence of the hematologic adverse reactions declines thereafter. Only a few cases of neutropenia, TTP, or aplastic anemia have arisen after more than 3 months of therapy. Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, patients receiving ticlopidine must, therefore, be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine should be immediately discontinued.

VII. Dosing and Administration

The usual dosing regimens for the platelet-aggregation inhibitors are listed in Table 11.

Table 11. Usual Dosing Regimens for the Platelet-Aggregation Inhibitors[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aspirin	Anti-inflammatory: 2.4-3.6 g per day in divided doses Carotid endarterectomy: 80 mg once daily to 650 mg twice daily Chronic stable angina pectoris: 75-325 mg once daily Coronary artery bypass graft: 325 mg once daily starting 6 hours postop Fever: 325-650 mg every 4-6 hours as needed; maximum, 4 g in	Analgesic/Antipyretic ≤12 years: Oral: 10-15mg/kg/dose every 4 hours up to 60-80 mg/kg/day. Analgesic/Antipyretic and 12 years and older: Oral: 325-1000 mg every 4-6 hours as needed; maximum: 4 g in 24 hours Juvenile rheumatoid arthritis: Oral: initial 90-130 mg/kg/day in divided doses; increase dose as needed for anti-inflammatory efficacy	Chewable tablet: 81 mg Packet: 650 mg Rectal suppository: 300 mg 600 mg Tablet: 81 mg 325 mg 500 mg Tablet (DR): 81 mg 325 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	24 hours Generalized aches and pains: 326-650 mg every 4 hours; maximum, 4 g in 24 hours Headache: 500-1,000 mg every 4-6 hours; maximum 4 g in 24 hours Ischemic Stroke/TIA: 50-325 mg once daily Myocardial infarction (acute): 160-325mg as soon as MI is suspected Myocardial infarction (prophylaxis): 75-325 mg once daily Osteoarthritis: Up to 3 g per day in divided doses Percutaneous transluminal coronary angioplasty: 325 mg 2 hours preoperatively and 160-325 mg daily postoperatively Rheumatoid arthritis: Initial, 3 g a day in divided doses; increase dose as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 µg/mL Spondyloarthropathies: Up to 4 g per day in divided doses Systemic lupus erythematosus, arthritis and pleurisy: Initial, 3 g a day in divided doses; increase dose as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL Unstable angina pectoris: 75-325 mg once daily	with target plasma salicylate levels of 150-300 mcg/mL	500 mg Tablet (SR): 800 mg
Aspirin and dipyridamole	Thromboembolic stroke, recurrent: prophylaxis: 1 capsule twice daily	Safety and efficacy in children have not been established.	Capsule (ER): 25/200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Alternative regimen for patients with intolerable headaches: 1 capsule at bedtime and low-dose aspirin in the morning; return to usual dose as soon as tolerance to headache develops (usually within a week)		
Cilostazol	Intermittent claudication: 100 mg orally twice daily	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg
Clopidogrel	Non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction): Initial, 300 mg once; maintenance, 75 mg orally once daily Recent myocardial infarction, recent stroke, or established peripheral arterial disease: 75 mg orally once daily ST-segment elevation acute myocardial infarction: 75 mg once daily, administered in combination with aspirin, with or without thrombolytics; clopidogrel may be initiated with or without a loading dose	Safety and efficacy in children have not been established.	Tablet: 75 mg 300 mg
Dipyridamole	Cardiac valve replacement, adjunct prophylaxis: Tablet: 75-100 mg 4 times daily as an adjunct to warfarin therapy Radionuclide myocardial perfusion study: Injection: 0.142 mg/kg/minute (0.57 mg/kg total) intravenously over 4 minutes prior to thallium; maximum 60 mg	Safety and efficacy in children below the age of 12 years have not been established.	Injection: 5 mg/ml Tablet: 25 mg 50 mg 75 mg
Prasugrel	Acute Coronary Syndrome: Tablet: 60 mg orally one time as a loading dose. For those weighing ≥60 kg, dose is 10 mg once daily. For those weighing ≤60 mg, dose is 5mg once daily. Should be taken with aspirin 75-325mg daily.	Safety and efficacy in children have not been established.	Tablet : 5mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Not recommended for use in patients >75 years of age.		
Ticlopidine	Coronary artery stent implantation, adjunct: Tablet: 250 mg twice daily together with antiplatelet doses of aspirin for up to 30 days of therapy following successful stent implantation Stroke: Tablet: 250 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 250 mg

DR=delayed-release, ER=extended-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the platelet-aggregation inhibitors are summarized in Table 12.

Table 12. Comparative Clinical Trials with the Platelet-Aggregation Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cerebrovascular Conditions				
International Stroke Trial[36] (1997) Aspirin 300 mg daily vs heparin 5,000 or 12,500 IU BID vs aspirin and heparin vs placebo	MC, OL, RCT Patients with acute ischemic stroke (randomized within 48 hours of stroke onset), 61% of patients were >70 years	N=19,435 Up to 14 days	Primary: Death from any cause within 14 days, death or dependency at 6 months Secondary: Symptomatic intracranial or extracranial hemorrhage, ischemic stroke or other major event within 14 days	Primary: Aspirin-allocated patients experienced slightly fewer deaths within 14 days (9.0% vs 9.4%; P=NS). There was a trend toward a reduction in death or dependence at 6 months (62.2% vs 63.5%; P=0.07; a difference of 13 per 1,000 patients) and after adjustment for baseline prognosis the benefit from aspirin was significant (P=0.03; a difference of 14 per 1,000 patients). More aspirin-allocated patients reported complete recovery from their stroke (17.6% vs 16.6%; P=0.07). Secondary: Aspirin-allocated patients had significantly fewer recurrent ischemic strokes within 14 days (2.8% vs 3.9%; P<0.001) with no significant excess of hemorrhagic strokes (0.9% vs 0.8%), so the reduction in death or nonfatal recurrent stroke with aspirin was significant (11.3% vs 12.4%; P=0.02; 11 fewer per 1,000 patients treated). Aspirin was associated with a significant excess of 5 transfused or fatal extracranial bleeds per 1,000 patients (1.1% vs 0.6%; P=0.0004), in the absence of heparin the excess was 2 and was not significant. There was no interaction between aspirin and heparin in the main outcomes.
CAST[37] (1997) Aspirin 160 mg daily vs	MC, PC, RCT Hospitalized patients with acute ischemic stroke (were randomized within 48 hours of stroke	N=21,106 Up to 4 weeks	Primary: Death from any cause during the 4-week treatment period, death or dependence at discharge	Primary: Patients in the aspirin group experienced a small but significant reduction in both early mortality (3.3% vs 3.9%; P=0.04) and recurrent ischemic strokes (1.6% vs 2.1%; P=0.01) but slightly more hemorrhagic strokes than placebo (1.1% vs 0.9%; P>0.1). At discharge, the aspirin-treated group experienced a smaller proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	onset), mean age 63 years		Secondary: Fatal or nonfatal recurrent stroke, death or nonfatal stroke during the scheduled treatment period	patients who were dead or dependent (30.5% vs 31.6%; P=0.08), corresponding to 11.4 fewer per 1,000 patients. Secondary: Fatal and nonfatal recurrent strokes occurred in 3.2% of aspirin-allocated patients vs 3.4% for placebo (P=NS). For the combined in hospital end point of death or nonfatal stroke at 4 weeks, there was a 12% proportional risk reduction with aspirin (5.3% vs 5.9%; P=0.03), an absolute difference of 6.8 fewer cases per 1,000 patients.
Diener et al.[38] (1996) ESPS 2 Aspirin 25 mg BID alone vs aspirin and dipyridamole ER 25-200 mg BID (Aggrenox®) vs dipyridamole ER 200 mg BID (not available in the United States) vs placebo	DB, PC, MC, RCT Male and female patients who had an ischemic stroke (76%) or TIA (24%) within 3 months prior to study entry, mean age 66.7 years	N=6,602 24 months	Primary: Stroke (fatal or nonfatal), death (all-cause mortality) and combined stroke or death Secondary: TIA, adverse events	Primary: In comparison to placebo, stroke risk was reduced by 18% with aspirin alone (P=0.013), 37% with the fixed-dose combination product of aspirin and ER dipyridamole (P<0.001) and 16% with dipyridamole alone (P=0.039). There was no significant difference in all-cause mortality among the active treatment groups. In comparison to placebo, the risk of stroke or death was reduced by 13% with aspirin alone (P=0.016), 24% with the fixed-dose combination (P<0.001) and 15% with dipyridamole alone (P=0.015). Secondary: Aspirin alone (P<0.001), the fixed-dose combination product (P<0.001) and dipyridamole alone (P<0.01) were significantly effective in preventing TIA compared to placebo. Headache was the most common adverse event, occurring more frequently in the dipyridamole-treated patients. All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received aspirin in comparison to placebo or dipyridamole.
Leonardi-Bee et	MA	N=11,036	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[39] (2005) Aspirin and dipyridamole vs dipyridamole vs aspirin alone vs control Two formulations of dipyridamole were assessed: conventional (daily dose 150-300 mg) and modified release (daily dose 400 mg). The daily dose of aspirin was 50-1,300 mg.	Patients with previous ischemic stroke and/or TIA	(5 trials) 15-72 months	Incidence of combined fatal and nonfatal stroke Secondary: Nonfatal stroke, combined fatal and nonfatal MI, vascular death, and composite of nonfatal stroke, nonfatal MI and vascular death	The incidence of recurrent stroke was reduced by dipyridamole as compared with control (OR, 0.82; 95% CI, 0.68 to 1.00; P<0.05), and by combined aspirin and dipyridamole vs aspirin alone (OR, 0.78; 95% CI, 0.65 to 0.93; P<0.05), dipyridamole alone (OR, 0.74; 95% CI, 0.60 to 0.90; P<0.05), or control (OR, 0.61; 95% CI, 0.51 to 0.71; P<0.05). Secondary: The combination of dipyridamole and aspirin also significantly reduced the composite outcome of nonfatal stroke, nonfatal MI, and vascular death as compared with aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97; P<0.05), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.90; P<0.05), or control (OR, 0.66; 95% CI, 0.57 to 0.75; P<0.05). The combination of dipyridamole and aspirin significantly reduced the incidence of fatal and nonfatal MI compared to control (P<0.05) but not compared to monotherapy with aspirin or dipyridamole (P>0.05). Vascular death was not altered in any group.
Sacco et al.[40] (2005) Aspirin and dipyridamole ER 25-200 mg BID (Aggrenox®) vs	DB, PC, MC, RCT (Post-hoc analysis of the ESPS 2 trial) Male and female patients who had an ischemic stroke (76%) or TIA (24%) within 3 months	N=1,650 (Aggrenox®) N=1,649 (aspirin)	Primary: Rates of annual strokes and combined strokes and vascular events	Primary: Compared to aspirin alone, aspirin plus ER dipyridamole was more effective in reducing the risk of stroke (relative risk reduction, 23%; P=0.006) and stroke or vascular events (relative risk reduction, 22%, P=0.003). A more pronounced efficacy was observed for patients <70 years; those with hypertension, prior MI, prior stroke or TIA, and any prior cardiovascular disease; and smokers (all P<0.01). The greatest relative

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin 25 mg BID	prior to study entry, mean age 66.7 years			hazard reduction (44.6%) was noted for patients with a stroke or TIA before the qualifying event. Significant hazard reductions were reported for the combined outcome of stroke or vascular events with the greatest reductions found in patients with prior stroke or TIA, previous MI and among current smokers. The difference in efficacy increased in higher-risk patients.
ESPRIT Study Group[41] (2006) ESPRIT Aspirin (30-325 mg daily) and dipyridamole ER (200 mg BID), either as a fixed-dose combination or individual components vs aspirin 30-325 mg daily	MC, OL, RCT Patients with a TIA or minor stroke	N=2,739 Mean follow-up 3.5 years	Primary: Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleeding complication (whichever happened first) Secondary: Death from all causes, death from all vascular causes, death from all vascular causes and nonfatal stroke, all major ischemic events, all vascular events, major bleeding complications	Primary: Primary outcome events occurred in 173 (13%) of patients on aspirin plus dipyridamole vs 216 (16%) on aspirin monotherapy (HR, 0.80; 95% CI, 0.66 to 0.98; absolute risk reduction 1.0% per year; 95% CI, 0.1 to 1.8). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs 184), mainly because of headache. Secondary: The hazard ratios for death from all causes and all vascular causes were 0.88 (95% CI, 0.67 to 1.17) and 0.75 (95% CI, 0.51 to 1.10). Ischemic events were less frequent in the combination group than in the monotherapy group (HR, 0.81; 95% CI, 0.65 to 1.01). Major bleeding complications arose in 35 patients allocated to aspirin and dipyridamole vs 53 patients allocated to aspirin alone, whereas minor bleeding was reported in 171 patients allocated to the combination regimen vs 168 patients allocated to aspirin (RR, 1.03; 95% CI, 0.84 to 1.25).
Verro et al.[42] (2008) Aspirin and dipyridamole (IR and ER formulations)	MA Patients with a history of non-cardioembolic stroke or TIA	N=7,648 (6 trials) Duration varied	Primary: Incidence of nonfatal stroke Secondary: Composite of stroke, MI or	Primary: Dipyridamole plus aspirin significantly reduced the risk of nonfatal ischemic and hemorrhagic stroke compared to aspirin alone (RR, 0.77; 95% CI, 0.67 to 0.89). Secondary: Dipyridamole plus aspirin significantly reduced the risk of the composite

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin			vascular death, subset analysis comparing outcomes with IR and ER dipyridamole	of stroke, MI or vascular death (RR, 0.85; 95% CI, 0.76 to 0.94). Based on 4 trials, IR dipyridamole plus aspirin did not show a statistically significant reduction in the risk of stroke (RR, 0.83; 95% CI, 0.59 to 1.15) or the composite outcome (RR, 0.95; 95% CI, 0.75 to 1.19) compared to aspirin alone. Based on 2 trials (ESPS 2 and ESPRIT), ER dipyridamole plus aspirin showed a significant reduction in risk for stroke (RR, 0.76; 95% CI, 0.65 to 0.89) and for the composite outcome (RR, 0.82; 95% CI, 0.73 to 0.92) compared to aspirin alone.
Sacco et al.[70] (2008) PROFESS Aspirin 25 mg and dipyridamole ER 200 mg twice daily vs clopidogrel 75 mg once daily	RCT, DB Patients ≥55 years of age with a recent ischemic stroke within 90 days of randomization	N=20,332 2.5 years	Primary: Recurrent stroke of any type Secondary: Composite of stroke, MI, or death from vascular causes	Primary: Of those in the ASA/dipyridamole group, 916 patients (9%) experienced a recurrent stroke compared with 898 patients (8.8%) in the clopidogrel group (HR, 1.01; 95% CI, 0.92 to 1.11). Secondary: Each group had 1,333 patients (13.1%) experience MI or death from a vascular cause (HR, 0.99; 95% CI, 0.92 to 1.07).
Markus et al.[43] (2005) CARESS Clopidogrel 300 mg on day 1 and then 75 mg QD on days 2-7 plus aspirin 75 mg QD vs	DB, PC, RCT Patients with ≥50% carotid stenosis	N=107 7 days	Primary: Proportion of patients who were MES positive on day 7 Secondary: Proportion of patients who were MES positive on day 2, the rate of embolization on both days 2 and 7	Primary: Intent-to-treat analysis revealed a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES positive on day 7, as compared with 72.7% of monotherapy patients (RR reduction, 39.8%; 95% CI, 13.8 to 58.0; P=0.0046). Secondary: MES frequency per hour was reduced compared with baseline by 61.4% (95% CI, 31.6 to 78.2; P=0.0013) in the dual-therapy group at day 7 and by 61.6% (95% CI, 34.9 to 77.4; P=0.0005) on day 2. There were 4 recurrent strokes and 7 TIAs in the monotherapy group vs no stroke and 4 TIAs in the dual-therapy group that were considered

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin 75 mg QD			and their percent change from baseline, safety	treatment emergent and ipsilateral to the qualifying carotid stenosis. MES frequency was greater in the 17 patients with recurrent ipsilateral events compared with the 90 without (P=0.0003).
Diener et al.[44] (2004) MATCH Clopidogrel 75 mg per day vs clopidogrel 75 mg and aspirin 75 mg per day	DB, PC, RCT High-risk patients with recent ischemic stroke or TIA and had at least one additional vascular risk factor who were already receiving clopidogrel	N=7,599 18 months	Primary: Composite of ischemic stroke, MI, vascular death or rehospitalization for an acute ischemic event Secondary: Death, stroke, individual components and various combinations of the primary end points	Primary: There was no significant benefit of combination therapy compared with clopidogrel monotherapy in reducing the primary outcome (15.7% vs 16.7%, respectively; P=0.244). Secondary: There was no significant benefit of combination therapy compared with clopidogrel alone in reducing the secondary outcomes. Life-threatening bleedings were higher in the group receiving aspirin and clopidogrel vs clopidogrel monotherapy (2.6% vs 1.3%; P<0.0001). Major and minor bleeding were also significantly higher with combination therapy vs clopidogrel monotherapy (both P<0.0001).
Kennedy et al.[45] (2007) FASTER Group 1 Clopidogrel 300 mg loading dose then 75 mg QD vs placebo Group 2 Simvastatin 40 mg QD	DB, PC, RCT Patients ≥40 years of age with TIA or minor stroke	N=392 90 days	Primary: Incidence of stroke (ischemic and hemorrhagic), safety (hemorrhage, myositis) Secondary: Composite of stroke, MI and vascular death	Primary: The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrollment rate because of increased use of statins. Within 90 days, 7.1% of patients on clopidogrel had a stroke compared to 10.8% of patients on placebo (RR, 0.7; 95% CI, 0.3 to 1.2) for an absolute risk reduction of –3.8% (95% CI, –9.4 to 1.9; P=0.19). In the simvastatin group, 10.6% of patients had a stroke within 90 days compared to 7.3% of patients on placebo (RR, 1.3; 95% CI, 0.7 to 2.4) for an absolute risk increase of 3.3% (95% CI, –2.3 to 8.9; P=0.25). Two patients on clopidogrel had intracranial hemorrhage compared with none on placebo (absolute risk increase 1.0%; 95% CI, –0.4 to 2.4; P=0.5). There was no difference between groups for the simvastatin safety outcomes. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients were also given aspirin 81 mg QD with a 162 mg loading dose if naïve to aspirin.				Clopidogrel was associated with a –3.3% risk difference in the secondary end point compared to placebo (95% CI, –9.3% to 2.7%; P=0.28). Simvastatin was associated with a +2.7% risk difference compared to placebo (95% CI, –3.2% to 8.7%; P=0.37).
Uchiyama et al.[33] (2009) Clopidogrel 75mg once daily vs ticlopidine 200 mg once daily	DB, RCT Japanese men 20-80 years of age with a history of cerebral infarctions	N=1,869 26 weeks and 52 weeks	Primary: Safety Secondary: Combined efficacy end point of cerebral infarction, MI, and vascular death	Primary: Significantly fewer patients experienced a safety event in the clopidogrel group than the ticlopidine group (P<0.001; HR, 0.610; 95% CI 0.529, 0.703). Almost twice as many patients in the ticlopidine group (25.6%) experienced hepatic dysfunction than in the clopidogrel group (13.4%). Secondary: There was no significant difference in the incidence of the combined efficacy endpoint between clopidogrel (2.6% of patients) and ticlopidine (2.5%). Clopidogrel was better tolerated than ticlopidine; there was no difference in the efficacy of the two products with regard to the secondary prevention of vascular events in patients with prior stroke.
Fukuuchi et al.[46] (2008) Ticlopidine 200 mg QD vs clopidogrel 75 mg QD	DB, DD, MC, RCT Japanese patients between the ages of 20 and 80 years who experienced a non-cardioembolic cerebral infarction at least 8 days prior to enrollment	N=1,151 52 weeks	Primary: Safety with emphasis on hematologic changes, hepatic dysfunction, nontraumatic hemorrhage and other serious adverse reactions	Primary: During the 52-week study period, 15.1% of ticlopidine patients and 7.0% of clopidogrel patients had at least one primary safety end point (P<0.001). Significant differences were primarily noted between ticlopidine and clopidogrel for hematologic disorders (2.4% vs 1.0%; P=0.043) and hepatic dysfunction (11.9% vs 4.2%; P<0.001). Study medication was discontinued prematurely due to safety end points in 27% and 17% of patients receiving ticlopidine and clopidogrel, respectively (P<0.001). The HR for the risk of discontinuing study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Combined incidence of nonfatal or fatal cerebral infarction or MI, or death due to other vascular causes	medication due to a primary safety end point was 0.559 (95% CI, 0.434 to 0.721) in favor of clopidogrel. Secondary: The incidence of vascular events did not differ significantly between ticlopidine and clopidogrel (2.6% vs 3.0%, respectively; P=0.948; HR, 0.977; 95% CI, 0.448 to 1.957).
Gent et al.[47] (1989) CATS Ticlopidine 250 mg BID vs placebo	DB, MC, PC, RCT Patients with ischemic strokes occurring from 1 week to 4 months	N=1,072 Up to 3 years	Primary: Event rate per year for stroke, MI, or vascular death Secondary: Adverse events	Primary: The event rate per year for stroke, MI or vascular death was 10.8% in the ticlopidine group and 15.3% in the placebo group. Compared to placebo, ticlopidine reduced the RR of stroke, MI or vascular death by 30% (P=0.006) in the on-treatment analysis and by 23% (P=0.020) using the intent-to-treat approach. Ticlopidine reduced the RR of ischemic stroke by 33% (P=0.008) in the on-treatment analysis. Ticlopidine was beneficial for both men and women (RR, 28.1%; P=0.037 and RR, 34.2%; P=0.045, respectively). Secondary: Adverse events associated with ticlopidine included neutropenia (severe in about 1% of cases), skin rash (severe 2%) and diarrhea (severe 2%).
Hass et al.[48] (1989) TASS Ticlopidine 250 mg BID vs aspirin 650 mg BID	Blinded, MC, RCT Patients with recent (within 3 months) minor stroke or TIA	N=3,069 2-6 years	Primary: Nonfatal stroke or death Secondary: Adverse events	Primary: Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate was 17% for ticlopidine vs 19% for aspirin; P=0.048). Ticlopidine reduced the risk of stroke after 3 years by 21% (10% for ticlopidine vs 13% for aspirin; P=0.024). Secondary: Ticlopidine significantly increased total cholesterol compared to aspirin (9% vs 2%; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group but bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. Severe neutropenia occurred in 0.9% of patients.
Gorelick et al.[49] (2003) AAASPS Ticlopidine 250 mg BID vs aspirin 325 mg BID	DB, MC, RCT African American men and women who recently had a non-cardioembolic ischemic stroke	N=1,809 Up to 2 years	Primary: Composite of recurrent stroke, MI, or vascular death Secondary: Fatal or nonfatal stroke	Primary: There was no statistically significant difference in the percent of patients reaching the primary outcome of recurrent stroke, MI or vascular death between ticlopidine and aspirin (14.7% vs 12.3%, respectively; P=0.12). Secondary: There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group (P=0.08). The frequency of laboratory-determined serious neutropenia was 3.4% for ticlopidine vs 2.2% for aspirin (P=0.12).
Combined Cardiovascular and Cerebrovascular Conditions				
Antithrombotic Trialists' Collaboration[50] (2002) Antiplatelet agents vs control vs one antiplatelet regimen versus another	MA Patients at high risk of occlusive vascular events	N=135,640 (287 trials) Duration varied	Primary: "Serious vascular event" (nonfatal MI, nonfatal stroke or vascular death)	Primary: Overall, antiplatelet therapy reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25%, and vascular mortality by 15% with no apparent adverse effect on other deaths. Aspirin was the most widely studied antiplatelet drug and low dose (75 to 150 mg daily) was at least as effective as higher daily doses for long-term use. In acute settings an initial loading dose of at least 150 mg aspirin may be required. Clopidogrel reduced serious vascular event by 10% compared with aspirin, which was similar to the 12% reduction observed with ticlopidine. The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone.
Sudlow et al.[32] (2009) Aspirin (325 mg	MA Patients at high risk for serious vascular	N=26,865 (10 trials) Duration	Primary: Composite outcome of stroke, MI, or death from	Primary: Treatment with clopidogrel or ticlopidine produced a modest reduction in the odds of a serious vascular event (11.6%) versus aspirin (12.5%; OR, 0.92; 95% CI, 0.85 to 0.99). This corresponds to the avoidance of 10

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for most studies) vs clopidogrel (75 mg once daily for most studies) or ticlopidine (250 mg twice daily for most studies)	events, including those with a previous TIA or ischemic stroke	varied	a vascular cause Secondary: Outcomes of adverse drug events	serious vascular events per 1000 patients treated with clopidogrel or ticlopidine rather than aspirin for an average of about two years. Secondary: Compared with aspirin, clopidogrel and ticlopidine significantly reduced gastrointestinal adverse effects. However, clopidogrel and ticlopidine increased the odds of skin rash and diarrhea, ticlopidine more than clopidogrel. Allocation to ticlopidine, but not clopidogrel, significantly increased the odds of neutropenia.
CAPRIE Steering Committee[51] (1996) CAPRIE Clopidogrel 75 mg QD vs aspirin 325 QD	DB, MC, PG, RCT Patients with recent ischemic stroke (within 6 months with at least a week of residual neurological signs), recent MI (within 35 days) or symptomatic peripheral arterial disease	N=19,185 1-3 years	Primary: Composite outcome of ischemic stroke, MI or vascular death Secondary: Primary outcome and amputation, vascular death, all-cause mortality, safety	Primary: Intention–to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI, or vascular death compared with 5.83% with aspirin, for a RR reduction of 8.7% (95% CI, 0.3 to 16.5; P=0.043) in favor of clopidogrel. Corresponding on-treatment analysis yielded a RR reduction of 9.4% in favor of clopidogrel. For the 6,431 patients admitted to the study with prior stroke, the RR reduction for ischemic stroke, MI, or vascular death was 7.3% in favor of clopidogrel (P=0.26), and the RR reduction for the end point of stroke was 8.0% (P=0.28). For the 6,302 patients admitted to the study with myocardial infarction, an RR increase of 3.7% was associated with clopidogrel (P=0.66). For the 6,452 patients admitted to the study with peripheral arterial disease, an RR of 23.8% was noted in favor of clopidogrel (P=0.0028). Secondary: Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (P=0.076). There was no significant difference between clopidogrel and aspirin with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				regards to vascular death (1.90% vs 2.06%; P=0.29) and all-cause mortality (3.05% vs 3.11%; P=0.71). There were no major differences in terms of safety. Severe rash (P=0.017) and severe diarrhea (P=0.080) were reported more frequently with clopidogrel and severe upper gastrointestinal discomfort (P=0.096), intracranial hemorrhage (P=0.23) and gastrointestinal hemorrhage (P=0.05) were reported more frequently with aspirin.
DeSchryver et al.[52] (2007) Dipyridamole with or without other antiplatelet drugs vs control (no drug or another antiplatelet drug)	MA Patients with arterial vascular disease (angina, CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA)	N=23,019 (29 trials) Duration varied	Primary: Secondary prevention of vascular death and vascular events (defined as vascular death or any death from an unknown cause, nonfatal stroke or nonfatal MI)	Primary: Compared with control, dipyridamole had no clear effect on vascular death (RR, 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole or type of presenting vascular disease did not influence this result. Compared with control, dipyridamole appeared to reduce the risk of vascular events (RR, 0.88; 95% CI, 0.81 to 0.95). This effect was only statistically significant in patients presenting with cerebral ischemia. There was no evidence that dipyridamole alone was more efficacious than aspirin.
Cardiovascular Conditions (Acute Coronary Syndrome, Myocardial Infarction, Angina Pectoris)				
CURE Trial Investigators[53] (2001) CURE Clopidogrel (300 mg immediately, followed by 75 mg once daily) plus aspirin vs aspirin	DB, PC, RCT Patients with NSTEMI, presenting within 24 hours of symptom onset	N=12,562 3-12 months	Primary: Composite of death from cardiovascular causes, nonfatal MI, or stroke (first primary outcome); composite of the first primary outcome or refractory ischemia (second primary outcome) Secondary: Severe ischemia,	Primary: A composite of death from cardiovascular causes, nonfatal MI, or stroke occurred in 9.3% of patients in the clopidogrel and aspirin group compared to 11.4% of patients in the aspirin group (RR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). When refractory ischemia was included with the first primary outcome, the composite rate was 16.5% in the clopidogrel and aspirin group compared to 18.8% for aspirin alone (RR, 0.86; 95% CI, 0.79 to 0.94; P<0.001). Secondary: Significant reductions in nonfatal MI (5.2% vs 6.7%) and trends toward reduction in death (5.1% vs 5.5%) and stroke (1.2% vs 1.4%) with clopidogrel plus aspirin versus aspirin alone were noted.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			heart failure, need for revascularization, safety	The percentages of patients with in hospital refractory or severe ischemia, recurrent angina, heart failure and revascularization procedures were also significantly lower with clopidogrel plus aspirin vs aspirin alone (all P<0.05). There were significantly more patients with major bleeding in the clopidogrel plus aspirin group than in the aspirin group (3.7% vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1% vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56; P=0.13).
COMMIT Collaborative Group[54] (2005) COMMIT Clopidogrel 75 mg plus aspirin 162 mg daily vs aspirin 162 mg daily	MC, PC, RCT Patients admitted to the hospital within 24 hours of suspected acute MI, mean age 61 years	N=45,852 15 days (mean)	Primary: Composite of death, reinfarction or stroke; death from any cause Secondary: Safety	Primary: Allocation to clopidogrel plus aspirin produced a highly significant 9% proportional reduction in death, reinfarction or stroke compared to aspirin alone (actual reductions 9.2% vs 10.1%, respectively; P=0.002), corresponding to 9 fewer events per 1,000 patients treated for about 2 weeks. There was also a significant 7% proportional reduction in any death in the clopidogrel plus aspirin group compared to aspirin alone (7.5% vs 8.1%; P=0.03). Secondary: Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel plus aspirin versus aspirin alone, either overall (0.58% vs 0.55%, respectively; P=0.59) or in patients older than 70 years or in those given fibrinolytic therapy.
Sabatine et al.[55] (2005) CLARITY-TIMI 28 Clopidogrel 300 mg loading dose, followed by 75 mg QD plus aspirin vs	DB, MC, PC, RCT Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI	N=3,491 30 days	Primary: Composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography (death or recurrent MI by day 8 or hospital discharge in	Primary: The primary end point was reached in 15.0% of patients receiving clopidogrel vs 21.7% for placebo, representing an absolute reduction of 6.7% in the rate and 36% in the odds of reaching the end point with clopidogrel therapy (95% CI, 27% to 47%; P<0.001). By 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1% to 11.6%; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin Patients received a fibrinolytic agent, and heparin when appropriate.			patients who did not undergo angiography) Secondary: Safety	Secondary: The rates of major bleeding and intracranial hemorrhage were similar in the two groups.
Bhatt et al.[56] (2006) CHARISMA Clopidogrel 75 mg QD plus aspirin 75-162 mg QD vs aspirin 75-162 mg QD	DB, MC, PC, RCT Patients 45 years of age or older with clinically evident cardiovascular disease (e.g., documented coronary, cerebrovascular or peripheral arterial disease) or multiple atherothrombotic risk factors	N=15,603 28 months	Primary: Composite of first occurrence of MI, stroke, or death from cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	Primary: The composite of MI, stroke or death from cardiovascular causes was 6.8% with clopidogrel plus aspirin and 7.3% with aspirin (RR, 0.93; 95% CI, 0.83 to 1.05; P=0.22). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel plus aspirin and 5.5% with aspirin alone (RR, 1.2; 95% CI, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel plus aspirin than aspirin alone (3.9% vs 2.2%; P=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel plus aspirin and 7.9% with aspirin alone (RR, 0.88; 95% CI, 0.77 to 1.00; P=0.046). Secondary: The secondary end point was reached in 16.7% and 17.9% (RR, 0.92; 95% CI, 0.86 to 1.00; P=0.04) of patients receiving clopidogrel plus aspirin vs aspirin alone, respectively. The rate of severe bleeding was 1.7% and 1.3% (RR, 1.25; 95% CI, 0.97 to 1.61; P=0.09) for patients receiving clopidogrel plus aspirin vs aspirin.
Hart et al.[57] (2008) CHARISMA Clopidogrel 75 mg QD plus aspirin 75-162 mg QD vs	DB, MC, PC, RCT (Post hoc analysis of participants with a history of atrial fibrillation in the CHARISMA trial) Patients 45 years of age or older with clinically evident	N=593 Median 28 months	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes Secondary: First occurrence of	Primary: There was no difference in the composite of stroke, MI or vascular death between patients receiving clopidogrel plus aspirin (35 of 298 patients) and aspirin alone (27 of 285 patients; P=0.40). Secondary: There was no difference in the composite of stroke, MI, vascular death or rehospitalization (70 vs 66 patients; P=0.93) or all-cause mortality (29 vs 25 patients; P=0.69) among patients receiving clopidogrel plus aspirin and aspirin alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin 75-162 mg QD	cardiovascular disease or multiple atherothrombotic risk factors; patients receiving oral anticoagulation were excluded		MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	Stroke (ischemic and hemorrhagic) occurred in 15 patients receiving clopidogrel plus aspirin (2.2% per year) and in 14 patients receiving aspirin alone (2.1% per year; HR, 1.03; 95% CI, 0.49 to 2.13; P=0.94). Severe or fatal extracranial hemorrhage occurred in 6 patients given clopidogrel plus aspirin vs 3 patients given aspirin alone (P=0.51), while intracranial bleeding occurred in 3 patients vs 1 patients (P=0.62), respectively.
Ho et al.[58] (2008) Clopidogrel (dose not specified)	RETRO Patients with ACS discharged on clopidogrel from Veterans Affairs hospitals	N=3,137 Duration varied	Primary: Rate of all-cause mortality or acute MI after stopping clopidogrel	Primary: Among medically treated patients, mean duration of clopidogrel treatment was 302 days. Death or acute MI occurred in 17.1% of patients, with 60.8% of events occurring during 0 to 90 days, 21.3% during 91 to 180 days, and 9.7% during 181 to 270 days after stopping treatment with clopidogrel. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping treatment with clopidogrel was associated with a significantly higher risk of adverse events (IRR, 1.98; 95% CI, 1.46 to 2.69 vs the interval 91-180 days). Among the PCI-treated patients with ACS, mean duration of clopidogrel treatment was 278 days and death or acute MI occurred in 7.9% of patients, with 58.9% of events occurring during 0 to 90 days, 23.4% during 91 to 180 days, and 6.5% during 181 to 270 days after stopping clopidogrel treatment. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping clopidogrel treatment was associated with a significantly higher risk of adverse events (IRR, 1.82; 95% CI, 1.17 to 2.83).
Wiviott et al.[28] (2007) TRITON-TIMI 38	MC, DB, AC, RCT Patients with moderate-to-high risk ACS (unstable	N=13,608 Mean 14.5 months	Primary: Composite of death from CV causes, nonfatal MI, or nonfatal stroke	Primary: Compared to clopidogrel, treatment with prasugrel was associated with a reduction in the composite primary efficacy endpoint of death from CV causes, nonfatal MI, or nonfatal stroke (9.9% vs 12.1%, respectively; HR, 0.81; 95% CI, 0.73-0.9; P<0.001). This difference was driven primarily by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clopidogrel 300 mg loading dose followed by 75mg daily plus aspirin 75-162 mg/daily vs prasugrel 60 mg loading dose followed by 10 mg daily plus aspirin 75-162 mg/daily	angina, NSTEMI, or STEMI) and scheduled PCI		Secondary: Stent thrombosis, composite of CV death, nonfatal MI, nonfatal stroke, or re-hospitalization due to cardiac ischemic event, 30 and 90 day event rates for the primary endpoint and composite of CV death, nonfatal MI, or urgent target vessel revascularization	a reduction in nonfatal MI, which was evident early on in therapy. Secondary: In a post-hoc analysis, probable or definite stent thrombosis was also significantly reduced in the prasugrel vs clopidogrel group (1.1% vs 2.4%; HR 0.48; 95% CI 0.36-0.64; P<0.001), a finding that was observed with both bare metal and drug eluding stents. The composite of CV death, nonfatal MI, nonfatal stroke, and re-hospitalization for ischemia was 12.3% for prasugrel compared to 14.6% for clopidogrel (HR, 0.78; 95% CI, 0.69-0.89). The improvement in efficacy outcomes with prasugrel was accompanied by an increased risk of bleeding compared to clopidogrel. A higher percentage of patients treated with prasugrel had major bleeding than those treated with clopidogrel (2.4% versus 1.8%; P=0.03). There was a significant increase in life-threatening bleeding with prasugrel and a significant increase in fatal bleeding (0.4% versus 0.1%; P=0.002) compared to clopidogrel.
Montalescot et al.[29] (2009) TRITON-TIMI 38 Clopidogrel 300 mg loading dose followed by 75mg daily plus aspirin 75-162 mg/daily vs prasugrel 60 mg loading dose followed by 10 mg	DB, DD, PG (Subgroup analysis of STEMI patients) Patients who presented within 12 hours of onset of symptoms of STEMI for whom primary PCI was planned	N=3,534 15 months	Primary: Composite of CV death, non-fatal MI, or non-fatal stroke Secondary: CV death, non-fatal MI, or urgent target vessel revascularization at 30 days	Primary: At 30 days, 115 (9.5%) individuals assigned prasugrel group had met the primary endpoint compared with 166 (9.5%) allocated to the clopidogrel group (HR 0.68 [95% CI 0.54–0.87]; P=0.0017). This effect continued to 15 months (174 [10·0%] vs 216 [12·4%]; 0.79 [0.65–0.97]; P=0.0221). Secondary: At 30 days, the secondary endpoints of CV death, MI, or urgent target vessel revascularization were significantly reduced with prasugrel (HR, 0.75; 95% CI, 0.59 to 0.96; P=0.0205) and 15 months (HR, 0.79; 0.65 to 0.97; P=0.0250), as was stent thrombosis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily plus aspirin 75-162 mg/daily				
Procedures and/or Surgery				
Leon et al.[65] (1998) Aspirin 325 mg QD vs aspirin 325 mg QD and warfarin (dose adjusted to INR 2.0-2.5) vs aspirin 325 mg QD and ticlopidine 250 mg BID	MC, RCT Patients undergoing stent implantation	N=1,653 30 days	Primary: Composite of death, revascularization of target lesion, angiographically evident thrombosis or MI within 30 days Secondary: Achievement of <50% residual stenosis without death or emergency bypass surgery, procedure-related MI, hematologic dyscrasias, hemorrhagic and vascular surgical complications	Primary: The primary end point was observed in 38 patients: 3.6% assigned to aspirin alone, 2.7% assigned to aspirin plus warfarin and 0.5% assigned to aspirin plus ticlopidine (P=0.001 for the comparison of all 3 groups). Secondary: Compared to aspirin alone, and aspirin plus warfarin, treatment with aspirin and ticlopidine resulted in a lower rate of stent thrombosis (P=0.001) following coronary stenting. Hemorrhagic complications occurred in 10 patients: 1.8% with aspirin alone, 6.2% with aspirin plus warfarin and 5.5% with aspirin plus ticlopidine (P<0.001 for the comparison of all 3 groups); the incidence of vascular surgical complications was 0.4%, 2.0% and 2.0%, respectively (P=0.02). There were no significant differences in the incidence of neutropenia or thrombocytopenia among the 3 treatment groups and the overall incidence was 0.3%.
Ahn et al.[69] (2008) CIDES Aspirin 100-200 mg and cilostazol 200 mg per day vs	MC, RCT Diabetic patients who underwent successful stenting	N=280 Mean 7.1 months	Primary: Change in luminal diameter Secondary: Rate of angiographic restenosis	Primary: The minimal luminal diameter at follow-up period for the aspirin and cilostazol group was 2.55 mm compared with 2.4 mm in the aspirin and clopidogrel group (P=NS). Secondary: The rate of angiographic restenosis (stent plus 5-mm borders) was 9 (8.0%) in the aspirin and cilostazol group and 20 (16.1%) in the aspirin and clopidogrel group (P=0.041).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin 100-200 mg and clopidogrel 75 mg per day				
Lee et al.[66] (2008) DECLARE-DIABETES Aspirin 200 mg daily and clopidogrel 300 mg loading dose, followed by 75 mg QD vs aspirin 200 mg daily, clopidogrel 300 mg loading dose, followed by 75 mg QD, and cilostazol 200 mg loading dose, followed by 100 mg BID	MC, PRO, RCT Diabetic patients ≥18 years of age undergoing drug-eluting stent implantation	N=400 9 months	Primary: In-stent late loss at 6 months Secondary: In-segment late loss and restenosis rate at 6 months; stent thrombosis, target vessel revascularization, major adverse cardiac events (death, MI, and target lesion revascularization) at 9 months; safety	Primary: At 6 months, the in-stent late loss was significantly lower in the triple therapy versus dual therapy group (0.25 mm vs 0.38 mm; P=0.025). Secondary: At 6 months, the in-segment late loss (0.42 mm vs 0.53 mm; P=0.031) and restenosis (8.0% vs 15.6%; P=0.033) were significantly lower in the triple therapy versus dual therapy group. At 9 months, there was no difference in the rate of stent thrombosis (0% vs 0.5%; P=0.999). Target vessel revascularization was lower in the triple therapy versus dual therapy group (3.5% vs 8.0%; P=0.053). At 9 months, major adverse cardiac events tended to be lower in the triple therapy than in the dual therapy group (3.0% vs 7.0%; P=0.066). Drug discontinuation was more common in the triple therapy vs dual therapy group (14.5% vs 2.5%; P<0.001) with skin rash and gastrointestinal disturbance the most common reasons for termination of cilostazol.
Han et al.[35] (2009) Aspirin 300 mg QD for 1 month, followed by 100 mg QD and clopidogrel 300-600 mg loading dose, followed by 75mg QD	SC, OL Patients aged 20-80 years admitted with ACS (unstable angina, NSTEMI, or STEMI) undergoing successful coronary stenting	N=1,212 12 months	Primary: Major adverse cardiac or cerebral event at one year (defined as the composite of cardiac death, nonfatal MI, stroke, or target vessel	Primary: Triple-antiplatelet treatment was associated with a significantly lower incidence of the primary end points (10.3% vs 15.1%; P=0.011). The need for target vessel revascularization was similar between patients who received triple- and dual-antiplatelet treatment (7.9% vs 10.7%; P=0.10). Multivariate analysis showed that female patients and clinically or angiographically high-risk patients benefited more from the triple-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 300 mg QD for 1 month, followed by 100 mg QD, clopidogrel 300-600 mg loading dose, followed by 75mg QD and cilostazol 100 mg BID			revascularization) Secondary: Bleeding events at one year	antiplatelet treatment. Secondary: There were no significant differences between the two regimens in terms of the risks for major and minor bleeding.
Jeong et al.[72] (2009) ACCEL-RESISTANCE Aspirin 200 mg QD, clopidogrel 75mg QD, and cilostazol 200 mg/day vs aspirin 200 mg QD and clopidogrel 150 mg QD	RCT Patients with high post-treatment platelet reactivity undergoing coronary stenting	N=60 30 days	Primary: Platelet function	Primary: After 30 days, significantly fewer patients in the triple versus high maintenance dose group had high post-treatment platelet reactivity (3.3% vs 26.7%, P=0.012). Percent inhibitions of 5 µmol/l ADP-induced Agg_{max} and late platelet aggregation (Agg_{late}) were significantly greater in the triple versus high maintenance group (51.1 +/- 22.5% vs 28.0 +/- 18.5%, P<0.001, and 70.9 +/- 27.3% vs 45.3 +/- 23.4%, P<0.001, respectively). Percent inhibitions of 20 µmol/l ADP-induced Agg_{max} and $Aggl_{ate}$ were consistently greater in the triple versus high maintenance dose group. Percent change of P2Y12 reaction units demonstrated a higher antiplatelet effect in the triple versus high maintenance dose group (39.6 +/- 24.1% vs 23.1 +/-29.9%, P=0.022).
Mehta et al.[60] (2001) PCI-CURE Aspirin and clopidogrel or placebo prior to	DB, RCT Patients with non-ST-elevation ACS from the CURE study undergoing PCI	N=2,658 Average duration of follow-up after PCI was 8 months	Primary: Composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of PCI (main primary	Primary: A total of 4.5% of patients in the clopidogrel and aspirin group reached the primary end point compared with 6.4% in the aspirin group (P=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularization (P=0.03) and of cardiovascular death or MI (P=0.047).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PCI; after PCI, stented patients received open-label clopidogrel or ticlopidine in combination with aspirin for 2-4 weeks; then clopidogrel or placebo was resumed (for 3-12 months after initial randomization)			end point); cardiovascular death or MI from time of PCI to scheduled end of trial	Overall, clopidogrel was associated with a 31% reduction in cardiovascular death or MI, including events before and after PCI (P=0.002). At follow-up, there was no significant difference in major bleeding between the groups (P=0.64).
Takeyasu et al.[64] (2005) Cilostazol 200 mg/day and aspirin 81-200 mg/day vs ticlopidine 200 mg/day and aspirin 81-200 mg/day	OL, RCT Patients with ischemic heart disease receiving stents	N=642 6 months	Primary: Rate of stenosis according to qualitative coronary angiography analysis of minimal lumen diameter of artery, safety	Primary: The rates of restenosis (27.8% vs 29.3%; P=NS) and target lesion revascularization (22.4% vs 23.5%; P=NS) were similar between patients receiving cilostazol and ticlopidine. The rate of subacute thrombosis was significantly greater with cilostazol than ticlopidine (2.5% vs 0.3%; P=0.02). There were no differences in the incidence of adverse reactions with the exception of purpura, which was reported more frequently with ticlopidine than cilostazol (1% vs 0.0%; P=0.045).
Sabatine et al.[59] (2005) PCI-CLARITY Clopidogrel (300 mg loading dose, followed by 75 mg QD) plus aspirin (150-325 mg on the first day and then 75-162 mg QD)	DB, MC, PC, RCT Patients with STEMI who received fibrinolytics and underwent PCI (after mandated angiography in CLARITY-TIMI 28)	N=1,863 30 days	Primary: Composite of cardiovascular death, recurrent MI or stroke from PCI to 30 days after randomization Secondary: MI or stroke before PCI and the primary end point	Primary: Pretreatment with clopidogrel in patients receiving concurrent aspirin significantly reduced the primary end point following PCI compared to aspirin alone (3.6% vs 6.2%; adjusted OR, 0.54; 95% CI, 0.35 to 0.85; P=0.008). Pretreatment with clopidogrel and aspirin also reduced the incidence of MI or stroke prior to PCI (4.0% vs 6.2%; OR, 0.62; 95% CI, 0.40 to 0.95; P=0.03). Secondary: Overall, pretreatment with clopidogrel significantly reduced the secondary

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo plus aspirin (150-325 mg on the first day and then 75-162 mg QD)			from randomization to 30 days	outcome (7.5% vs 12.0%; adjusted OR, 0.59; 95% CI, 0.43 to 0.81; P=0.001). There was no significant excess in the rates of major or minor bleeding in patients receiving dual therapy vs aspirin alone (2.0% vs 1.9%, respectively; P>0.99).
Steinhubl et al.[61] (2002) CREDO Clopidogrel 300 mg loading dose (3-24 hours before PCI), then clopidogrel 75 mg QD through 12 months vs placebo (3-24 hours before PCI), then clopidogrel 75 mg QD through day 28, then placebo through 12 months All patients received aspirin 325 mg prior to PCI, then 325 mg QD through day 28, then 81-325 mg QD thereafter.	DB, MC, PC, RCT Patients undergoing PCI	N=2,116 12 months	Primary: One-year incidence of the composite of death, MI, or stroke; 28-day incidence of the composite of death, MI or urgent target vessel revascularization Secondary: Components of composite end points, administration of clopidogrel <6 hours or ≥6 hours before PCI, need for target vessel revascularization or any revascularization at 1 year	Primary: Long-term (1 year) clopidogrel and aspirin therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke versus aspirin alone (95% CI, 3.9% to 44.4%; P=0.02; absolute reduction, 3%). Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI or urgent revascularization at 28 days (–18.5%; 95% CI, –14.2% to 41.8%; P=0.23). Secondary: A similar level of benefit was found in the individual components of the primary end point at 1 year, although individual outcomes were not significant. Treatment randomization did not appear to influence the rate of target vessel revascularization or any other revascularization during the follow-up period. In a prespecified subgroup analysis, patients who had received clopidogrel at least 6 hours before PCI experienced a reduction in the relative combined risk of death, MI, or stroke by 38.6% (95% CI, –1.6% to 62.9%; P=0.051) compared with no reduction when treatment was given less than 6 hours before PCI (P=0.051). Risk of major bleeding at 1 year increased, but not significantly (8.8% with clopidogrel vs 6.7% with aspirin alone; P=0.07).
Lev et al.[62] (2008)	PRO	N=292	Primary: Occurrence of	Primary: TIMI myocardial perfusion grade 3 occurred in a higher proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clopidogrel 300-600 mg before PCI vs clopidogrel 300-600 mg immediately after PCI Patients were treated with aspirin before PCI, then aspirin and clopidogrel 75 mg QD for 3-12 months after PCI	Patients with chest pain and STEMI undergoing emergency PCI I.	6 months	TIMI myocardial perfusion grade 3 after PCI Secondary: Incidence of reinfarction, stent thrombosis, target vessel revascularization, death	patients in the clopidogrel pretreatment group than in the no pretreatment group (85% vs 71%; P=0.01). Secondary: The incidence of reinfarction at 30 days (0% vs 3.2%, respectively; P=0.04) and 6 months (0.6% and 3.9%, respectively; P=0.09) was lower in the pretreatment group than in the no pretreatment group. The incidence of stent thrombosis at 30 days (0% vs 2.4%, respectively; P=0.08) and 6 months (0% and 3.9%, respectively; P=0.02) was lower in the pretreatment group than in the no pretreatment group. The incidence of death and target vessel revascularization were not significantly different between the 2 groups at 30 days (P=0.6 and P=1.0) or 6 months (P=0.7 and P=0.9).
Bertrand et al.[63] (2000) CLASSICS Clopidogrel 300 mg loading dose then 75 mg QD and aspirin 325 mg QD vs clopidogrel 75 mg QD and aspirin 325 mg QD vs ticlopidine 250 mg BID and aspirin 325	RCT Patients receiving a stent placement	N=1,020 28 days	Primary: Major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation due to noncardiac adverse event Secondary: Incidence of cardiac events	Primary: Primary end point occurred in 4.6% of patients in the combined clopidogrel group and in 9.1% of patients in the ticlopidine group (RR 0.50; 95% CI, 0.31 to 0.81; P=0.005). Secondary: Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (1.2% with clopidogrel loading dose, 1.5% with clopidogrel without the loading dose and 0.9% with ticlopidine; P=NS for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD				
Gao et al.[30] (2009) Clopidogrel 75mg/day and aspirin 100 mg/day vs clopidogrel 75mg/day	RCT Patients undergoing elective CABG	N=197 12 months	Primary: CABG graft patency rates	Primary: At 1 month and 12 months after CABG graft patency rates of clopidogrel monotherapy group were, respectively, 99.0% and 96.9% for the left internal mammary artery (LIMA) and 98.1% and 93.5% for the saphenous vein grafts. Those of the dual antiplatelet therapy group were, respectively, 98.9% and 97.8% for LIMA, and 98.2% and 96.3% for saphenous vein grafts. Thus, there were no significant differences in graft patency between the two groups (p >0.05).
Park et al.[31] (2010) Clopidogrel 75mg/day and aspirin (100-200 mg per day) vs aspirin 100-200 mg/day	OL Patients who had undergone drug eluting stent implantation ≥12 months prior to enrollment, who had not had a major cardiovascular event, or major bleeding since implantation	N=2,701 Mean 19.2 months	Primary: First occurrence of MI or death from cardiac causes after assignment to a treatment group Secondary: Death from any cause	Primary: The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy, as compared with 1.2% with aspirin monotherapy (HR, 1.65; 95% CI, 0.80 to 3.36; P=0.17). Secondary: There was no significant difference between the two treatment groups in the risk of individual secondary end points. In the dual antiplatelet therapy group as compared with the aspirin-monotherapy group, there was a nonsignificant increase in the composite risk of myocardial infarction, stroke, or death from any cause (hazard ratio, 1.73; 95% CI, 0.99 to 3.00; P=0.051) and in the composite risk of myocardial infarction, stroke, or death from cardiac causes (HR, 1.84; 95% CI, 0.99 to 3.45; P=0.06).
Sibbing et al.[71] (2009) Clopidogrel 75 mg daily vs pantoprazole vs	CS, OB Patients on maintenance clopidogrel therapy scheduled for a coronary angiography who were also taking a PPI at the time point of platelet function testing	N=1,000 Variable duration	Primary: Platelet aggregation in patients treated with pantoprazole Secondary: Platelet aggregation in patients treated with omeprazole or esomeprazole	Primary: Those treated with pantoprazole (p=0.88) had similar platelet aggregation compared to those not treated with a PPI. Secondary: Those treated with omeprazole experienced significantly higher platelet aggregation compared to patients without PPI treatment (p=0.001). Those treated with esomeprazole (p=0.69) had similar platelet aggregation compared to those not treated with a PPI.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
omeprazole vs esomeprazole				
Peripheral Artery Disease				
Berger et al.[34] (2009) Aspirin vs aspirin/ dipyridamole vs placebo	MA Patients with peripheral arterial disease	N=5,269 (18 trials) Duration varied	Primary: Relative risk reduction of aspirin therapy on the composite end point of nonfatal MI, nonfatal stroke, and cardiovascular death Secondary: All-cause mortality and each component of the primary end point	Primary: There was no overall statistically significant difference in the composite outcome of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death between the aspirin and placebo or control groups (RR 0.88, 95% CI: 0.76, 1.04, 18 RCTs). There was a significantly lower incidence of nonfatal stroke in the aspirin groups (RR 0.66, 95% CI: 0.47, 0.94, 18 RCTs). Secondary: There were no statistically significant differences between the groups for any other secondary efficacy outcome. There was no statistically significant difference between the groups in incidence of major bleeding, but this was not formally assessed in many included RCTs.
Hiatt et al.[67] (2008) CASTLE Cilostazol 50-100 mg BID vs placebo	DB, MC, PA, PC, RCT Patients ≥17 years with a clinical diagnosis of PAD and symptoms of claudication	N=1,435 Up to 3.5 years	Primary: All-cause mortality on treatment (defined as period while taking the study drug and for 30 days after discontinuing therapy) Secondary: Safety	Primary: Long-term adherence to cilostazol was poor with >60% of participants discontinuing therapy by 36 months. There were 18 deaths in patients receiving cilostazol (N=717) and 19 deaths in patients receiving placebo (N=718) (HR, 0.99; 95% CI, 0.52 to 1.88). The study was underpowered to meet its primary end point. In the full intent-to-treat population at 36 months, there were 49 deaths for cilostazol patients and 52 deaths for placebo patients (HR, 0.94; 95% CI, 0.64 to 1.39). Thus most deaths occurred >30 days after study drug discontinuation. The incidence of cardiovascular deaths was similar between the 2 groups (14 patients in each group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Serious bleeding events affected 18 patients taking cilostazol and 22 patients taking placebo. The rates of bleeding events were similar in patients who used aspirin, aspirin plus clopidogrel or anticoagulants at anytime during the course of the study.

Drug regimen abbreviations: BID=twice daily, ER=extended release, IR=immediate release, QD=once daily
Study abbreviations: CI=confidence interval, CS=cross sectional, DB=double-blind, DD=double-dummy, HR=hazard ratio, IRR=incidence rate ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OB=observational, OL=open-label, OR=odds ratio, PA=parallel arm, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SC=single center, IU=international units
Other abbreviations: AAASPS=American Aspirin Stroke Prevention Study, AC=active comparator, ACS=acute coronary syndrome, CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, CAST=Chinese Acute Stroke Trial, CATS=Canadian American Ticlopidine Study, CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, CARESS=Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis, CASTLE=Cilostazol: A STudy in Long-term Effects, CHARISMA=Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance, CLARITY-TIMI 28=Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 study, CLASSICS=Clopidogrel Aspirin Stent International Cooperative Study, COMMIT=ClOpidogrel and Metoprolol in Myocardial Infarction Trial, CURE=Clopidogrel in Unstable Angina to Prevent Recurrent Events, CREDO=Clopidogrel for the Reduction of Events During Observation, ESPRIT=European/Australasian Stroke Prevention in Reversible Ischemia, ESPS=European Stroke Prevention Study, FASTER=Fast Assessment of Stroke and TIA to prevent Early Recurrence, INR=international normalized ratio, MATCH=Management of ATherothrombosis with Clopidogrel in High-risk patients, MES=microembolic signal, MI=myocardial infarction, NSTEMI=non-ST-elevation myocardial infarction, PCI=percutaneous coronary intervention, PCI-ClARITY=PCI-Clopidogrel as Adjunctive Reperfusion Therapy, PCI-CURE=PCI-Clopidogrel in Unstable angina to prevent Recurrent Events, STEMI=ST-elevation myocardial infarction, TASS=Ticlopidine Aspirin Stroke Study, TIA=transient ischemic attack

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 13. Relative Cost of the Platelet-Aggregation Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aspirin	chewable tablet, delayed-release tablet, packet, rectal suppository, sustained-release tablet, tablet	Ecotrin®*‡, Stanback Analgesic®‡, Zorprin CR®	$	$
Aspirin and dipyridamole	extended-release capsule	Aggrenox®	$$$$	N/A
Cilostazol	tablet	Pletal®*	$$$	$$
Clopidogrel	tablet	Plavix®	$$$$	N/A
Dipyridamole	injection, tablet	Persantine®*	$$$-$$$$	$-$$
Prasugrel	tablet	Effient®	$$$$	N/A
Ticlopidine	tablet	N/A	N/A	$

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

X. Conclusions

The platelet-aggregation inhibitors play a major role in the management of cardiovascular, cerebrovascular and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes, angina, intermittent claudication, myocardial infarction, stroke and transient ischemic attack.[1-9] They are also approved for the prevention of thrombosis in patients undergoing cardiovascular procedures and/or surgery. Aspirin, cilostazol, dipyridamole and ticlopidine are available in a generic formulation. Aspirin is also available over-the-counter. The fixed-dose combination of aspirin/dipyridamole (Aggrenox®) is not interchangeable with the generic formulations of aspirin and dipyridamole since the strengths and delivery mechanisms are different among these products.

There are numerous guidelines that incorporate the use of the platelet-aggregation inhibitors. Aspirin has been the most frequently studied platelet-aggregation inhibitor and is usually the reference drug to which other treatments are compared.[50] It is recommended for the primary prevention of cardiovascular disease in men 45 to 79 years of age and in women 55 to 79 years of age.[10] Aspirin is also recommended for the treatment of acute coronary syndromes (ACS), chronic stable angina, peripheral artery disease, non-cardioembolic stroke, transient ischemic attack (TIA), and for the secondary prevention of coronary artery disease.[11-26,73] For patients who have experienced a non-cardioembolic stroke or TIA, treatment with aspirin, the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy.[23-25] However, the combination of aspirin and extended-release dipyridamole or clopidogrel monotherapy are suggested over aspirin monotherapy. Dual antiplatelet therapy with aspirin and clopidogrel is recommended for the treatment of non-ST-segment elevation ACS, ST-segment elevation myocardial infarction, and for the treatment of patients who undergo percutaneous coronary intervention (PCI) with stenting[12,15-19,21-22,73] The optimal duration of clopidogrel therapy in ACS is unknown.[6] Prasugrel was approved by the FDA in July 2009; therefore, the majority of the guidelines do not provide recommendations regarding the use of this agent. However, the 2009 ACC/AHA guidelines recommend aspirin in combination with either clopidogrel or prasugrel for patients with ST-segment elevation myocardial infarction who undergo PCI with stenting and do not give preference to one regimen over another.[16] This was largely due to increase rates of bleeding in the prasugrel group, the fact that only one large trial comparing the two products has been completed, and there is little experience with prasugrel in community practice at the time the guidelines were published. Cilostazol is only recommended for patients with moderate-to-severe disabling intermittent claudication who do not respond to exercise therapy, and who are not candidates for surgical or catheter-based intervention.[25-26]

A variety of clinical trials have assessed the effects of the platelet-aggregation inhibitors on cardiovascular, cerebrovascular and peripheral artery disease outcomes.[28-72] In patients with a history of ischemic stroke or TIA, treatment with the combination of aspirin and extended-release dipyridamole, clopidogrel monotherapy, or ticlopidine monotherapy significantly decreased thrombotic events compared to aspirin monotherapy.[38-42,47-48,51] In the PROFESS trial, there was no significant difference in the rate of recurrent stroke with clopidogrel compared to the combination of aspirin and extended-release dipyridamole.[70] Dipyridamole monotherapy has been shown to reduce stroke recurrence compared to placebo, but has not been shown to be more effective than aspirin monotherapy.[38-39] Treatment with the combination of clopidogrel and aspirin significantly decreased morbidity and mortality in patients with ACS compared to aspirin monotherapy.[53-55] The TRITON-TIMI 38 trial compared the efficacy and safety of clopidogrel or prasugrel in combination with aspirin in patients with ACS undergoing PCI.[28] Treatment with prasugrel was associated with a significant reduction in the composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke compared to clopidogrel. Overall mortality did not differ among the treatment groups. Stent thrombosis occurred in 2.4% of patients treated with clopidogrel and 1.1% of patients receiving prasugrel. Significantly more patients treated with prasugrel had major bleeding, including life-threatening and fatal bleeding, compared to patients who received clopidogrel.

The effectiveness of clopidogrel is dependent on its activation to an active metabolite by CYP2C19.[6] Clopidogrel forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Consider alternative treatments in patients identified as CYP2C19 poor metabolizers. Prasugrel can cause significant bleeding and should not be used in patients with active bleeding or a history of TIA or stroke.[8] It is also not recommended in patients ≥75 years of age due to the increased risk of fatal and intracranial bleeding and because of uncertain benefit, except in high-risk situations. Because ticlopidine is associated with a risk of

life-threatening blood dyscrasias, it should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.[1-3]

Therefore, all brand platelet-aggregation inhibitors 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. Clopidogrel (Plavix®) and the fixed-dose combination of aspirin and extended-release dipyridamole (Aggrenox®) should be available as first-line therapy through the medical justification portion of the prior authorization process for patients who have experienced an ischemic stroke or TIA. Clopidogrel (Plavix®) and prasugrel (Effient®) should be available as first-line therapy (in combination with aspirin) through the medical justification portion of the prior authorization process for patients who have experienced an acute coronary syndrome who are going to be managed medically or with percutaneous coronary intervention.

XI. Recommendations

No brand platelet-aggregation 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiarrhythmic Agents
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I. Overview

Cardiac contractions are regulated by electrical activity in the heart originating in the sinoatrial node and propagated through ion channels, chiefly sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) channels. Arrhythmias are caused by abnormalities in formation and transmission of impulses and are classified based on their origin: supraventricular (atrial or atrioventricular junction) or ventricular.[1]

Research in recent years has provided extensive data regarding the cellular mechanisms by which some of the antiarrhythmic drugs exert their action; however, the general approach to antiarrhythmic therapy remains largely empirical.[3] The antiarrhythmic agents are generally grouped into specific categories or classes based on their predominant mechanisms: (1) sodium channel blockade, (2) blockade of sympathetic autonomic effects in the heart, (3) prolongation of the effective refractory period, and (4) calcium channel blockade.[1] E. M. Vaughan Williams proposed the first antiarrhythmic classification system in 1970 and it is now the most widely used scheme. The Vaughan Williams classification system divides the antiarrhythmic agents into the following classes: Class I: fast sodium channel blockers, Class II: β-blockers, Class III: repolarization potassium current blockers, Class IV: calcium channel antagonists.[3] The agents included in this review differ with regards to their FDA-approved indications, mechanism of action, pharmacokinetic properties, drug interactions and adverse events.

The antiarrhythmic agents that are included in this review, as well as their Vaughan Williams Classifications, are listed in Table 1. This review encompasses all dosage forms and strengths. All of the antiarrhythmic agents are available in a generic formulation, with the exception of dofetilide and dronedarone. This class was last reviewed in May 2008.

Table 1. Antiarrhythmic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Vaughan Williams Classification	Current PDL Agent(s)
Amiodarone	injection, tablet	Cordarone®*, Pacerone®*	III	amiodarone
Disopyramide	capsule, sustained-release capsule	Norpace®*, Norpace CR®*	IA	disopyramide, Norpace®*, Norpace CR®*
Dofetilide	capsule	Tikosyn®	III	none
Dronedarone	tablet	Multaq®	I, II, III, IV	none
Flecainide	tablet	Tambocor®*	IC	flecainide
Mexiletine	capsule	N/A	IB	mexiletine
Propafenone	sustained-release capsule, tablet	Rythmol®*, Rythmol SR®	IC	propafenone
Quinidine	injection, sustained-release tablet, tablet	N/A	IA	quinidine

*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 treatment guidelines that incorporate the use of the antiarrhythmic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antiarrhythmic Agents

Clinical Guideline	Recommendation(s)
Institute for Clinical Symptoms Improvement (ICSI): **Atrial Fibrillation**[19] **(2008**)	General Considerations • The goals of therapy in the management of atrial fibrillation include relief of symptoms, prevention of stroke, and prevention of tachycardia-mediated cardiomyopathy. • The use of antiarrhythmics should be individualized based on the patient's comorbidities, cardiac history and potential risk for side effects. • Optimal antiarrhythmic drug therapy should be effective in reducing symptoms, preventing recurrent atrial fibrillation and should have low incidence of toxicity and proarrhythmia. • All antiarrhythmics used to convert atrial fibrillation/atrial flutter to sinus rhythm can cause serious complications, including torsades de points. • Due to the potential of antiarrhythmics to accelerate ventricular rate, rate control must be established before antiarrhythmic agents are initiated. Acute Rate Control • β-blockers are preferred for pharmacologic rate control, especially in patients with atrial fibrillation and heart failure. • Calcium channel blockers are alternative rate control agents when β-blockers are contraindicated. • Digoxin is a third-line agent for rate control. Digoxin does not lower blood pressure and has a positive inotropic effect. However, it works more slowly than β-blockers and calcium channel blockers, has no effect on the sympathetically mediated enhancement of atrioventricular node conduction during exercise, and is no better than placebo for conversion to normal sinus rhythm. • Amiodarone is a first-line agent for patients with decompensated heart failure. Antiarrhythmic/Chemical Cardioversion • All antiarrhythmics used to treat atrial fibrillation/atrial flutter can cause serious complications including the life-threatening arrhythmia torsades de pointes. • Pharmacologic therapy aimed at restoring sinus rhythm is often helpful in patients with atrial fibrillation. • Agents with proven efficacy for pharmacological cardioversion of atrial fibrillation of up to seven days duration include dofetilide, flecainide, ibutilide, propafenone and amiodarone. • Agents with proven efficacy for pharmacological cardioversion of atrial fibrillation for more than seven days include dofetilide, amiodarone and ibutilide. Failed Cardioversion Treatment Options • If initial attempts to restore normal sinus rhythm for atrial fibrillation fail, cardioversion can be repeated following a parenteral or oral loading dose of an appropriate antiarrhythmic agent. This approach should be avoided in patients with ejection fractions <30% because of the increased risk of torsades de pointes. Maintenance of Sinus Rhythm Following Conversion • Several antiarrhythmic drugs have been demonstrated to improve sinus rhythm maintenance following cardioversion, including amiodarone,

Clinical Guideline	Recommendation(s)
	propafenone, disopyramide, sotalol, flecainide, dofetilide and quinidine. • Flecainide, propafenone and sotalol are recommended to maintain normal sinus rhythm in patients with no (or minimal) heart disease, followed by amiodarone or dofetilide. • Flecainide, propafenone and sotalol are recommended to maintain normal sinus rhythm in patients with hypertension and no evidence of left ventricular hypertrophy, followed by amiodarone and dofetilide. • Amiodarone is recommended to maintain normal sinus rhythm in patients with hypertension who have evidence of substantial left ventricular hypertrophy. • Dofetilide and sotalol are recommended to maintain normal sinus rhythm in patients with coronary artery disease, followed by amiodarone. • Amiodarone and dofetilide are recommended to maintain normal sinus rhythm in patients with heart failure. • For the older patient >65 years of age, rate control is an equal strategy to rhythm control for long-term management of atrial fibrillation.
North American Society of Pacing and Electrophysiology/ Heart Rhythm Society (HRS): **A Practical Guide for Clinicians Who Treat Patients With Amiodarone**[14] **(2007)**	Ventricular Arrhythmias • Oral amiodarone is the recommended agent of choice for use in combination with additional appropriate therapies, including β-blockers, in patients with sustained ventricular tachyarrhythmias associated with structural heart disease, especially those with left ventricular dysfunction (LVD), and who are not candidates for an implantable cardioverter-defibrillator (ICD). • It is recommended that amiodarone therapy be reserved for symptomatic patients with non-sustained ventricular tachyarrhythmias that are refractory to β-blocker therapy and concerning enough to require treatment. Atrial Fibrillation (AF) • This guideline refers to the recommendations provided by the ACC/AHA/ESC 2006 guidelines that recommend oral amiodarone be used for treatment of AF in particular subsets of patients including: 1) patients post-myocardial infarction (MI) who are not candidates for sotalol or dofetilide; 2) those with congestive heart failure (CHF) and LVD who are not candidates for dofetilide; 3) patients with significant left ventricular (LV) hypertrophy, and 4) those symptomatic patients who are refractory to antiarrhythmic treatments and an alternative to catheter ablation is preferred. • Amiodarone therapy should only be considered in those patients with AF who need ventricular rate control and have failed or are unable to use other appropriate agents including digoxin, β-blockers, or calcium channel blockers. • If prophylactic amiodarone therapy is to be used prior to aortocoronary bypass surgery, it is recommended to only consider this therapy in those patients that are high-risk (prior history of AF, valve replacement surgery) and therapy with β-blocker monotherapy will most likely still be associated with a high post-operative AF occurrence rate. Pregnant Patients • Due to some unfavorable characteristics possessed by amiodarone, including end-organ toxicity, therapy with it in pregnant patients is not recommended unless there are no other treatment options available. Pediatric Patients • There is a lack of data studying intravenous (IV) amiodarone in pediatric patients, however, in some lethal tachyarrhythmias,

Clinical Guideline	Recommendation(s)
	amiodarone is often used in these situations. • It is recommended that children receiving amiodarone therapy be supervised by a pediatric electrophysiologist. Patient Follow-Up • Patient follow-up is recommended for patients receiving amiodarone therapy for either atrial or ventricular arrhythmias. • Follow-up recommendations include continued assessment of drug therapy, efficacy and toxicities. • It is recommended that follow-up evaluations with patients on amiodarone take place with personnel who are experienced with the agent. • It is recommended that initial assessments occur every 3-6 months to ensure efficacy and safety of the medication and arrhythmia stability. Following the initial period, follow-up assessments may occur every 6 months. Pulmonary Toxicity • Pulmonary toxicity is a well-known adverse event associated with amiodarone therapy. It is recommended that a pulmonologist be consulted when: 1) there is an abnormal chest radiography at baseline or follow-up; 2) there is an abnormal pulmonary function test value (particularly forced vital capacity and [D_LCO]) at baseline or follow-up evaluation; and/or 3) a new cough and/or dyspnea, especially if otherwise unexplained or unexpected. • It is recommended that all patients who are referred to a pulmonologist undergo full pulmonary function testing and high-resolution computed tomography (CT) scanning of the chest. Effects on Thyroid Function • Amiodarone is known to have adverse effects on thyroid function, either by causing hypo- or hyperthyroidism. It is recommended that an endocrinologist be consulted: 1) any time hyperthyroidism is suspected, even if suppression of thyroid-stimulating hormone (TSH) is mild and subclinical disease is possible; 2) an acutely ill patient where interpretation of thyroid function tests will be complicated by euthyroid sick syndrome; and/or 3) when considering treating subclinical hypothyroidism. • It is recommended to discontinue amiodarone therapy, if possible, in those patients who have underlying thyroid disease and treat them with high-doses of antithyroid drugs. The decision to discontinue amiodarone therapy should be based on the patient's cardiac needs. Follow-Up Visits • A history of complaints from the patient should be noted. In patients with ICDs, amiodarone therapy should not be altered without the involvement of an electrophysiologist or a cardiologist in charge of device follow-up. • A physical examination with documentation should be performed. If visual changes are reported, an examination by an ophthalmologist is required. • The following are recommended baseline tests that should be performed: liver function tests, thyroid function tests, chest x-ray, ophthalmologic evaluation, pulmonary function tests, high-resolution CT scan, and an electrocardiogram. The follow-up evaluation should include, at minimum, a yearly electrocardiogram and chest x-ray and semiannual thyroid tests and liver enzymes. Amiodarone levels may be obtained after dose adjustments or to help determine if the dose may be decreased.

Clinical Guideline	Recommendation(s)
	When to Refer to an Electrophysiologist • Refer when worsening arrhythmia symptoms. • Refer when evidence of amiodarone toxicity requiring changes in drug dosing or drug discontinuation. Until the arrhythmia problem stabilizes, the patient may require intensive monitoring, electrophysiologic testing, ablative therapy, or pacemaker or ICD implantation. • Repeat defibrillation threshold testing is recommended for patients with an ICD due to the drugs effect of increasing this threshold. • Assess amiodarone-induced slowing of ventricular tachyarrhythmias rate in patients with an ICD such that ventricular tachyarrhythmias would not be detected by the device and therapy not delivered. • Refer for pregnant patients who require amiodarone. • Refer for pediatric patients who require amiodarone.
American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC): **Guidelines for Management of Patients with Atrial Fibrillation[15] (2006)**	Heart Rate Control Versus Rhythm Control • The initial and subsequent management of symptomatic atrial fibrillation may differ from one patient to another. • Depending upon symptoms, rate control may be reasonable initial therapy in older patients with persistent atrial fibrillation who have hypertension or heart disease. • For younger individuals, especially those with paroxysmal lone atrial fibrillation, rhythm control may be a better initial approach. • Often medications that exert both antiarrhythmic and rate-controlling effects are required. • The AFFIRM trial found no difference in mortality or stroke rate between patients assigned to one strategy or the other. • The RACE trial found rate control not inferior to rhythm control for prevention of death and morbidity. • Patients at high risk for stroke may require anticoagulation regardless of whether the rate-control or rhythm-control strategy is chosen. Pharmacological Rate Control During Atrial Fibrillation • Measurement of the heart rate at rest and control of the rate using pharmacological agents (either a β-blocker or nondihydropyridine calcium channel antagonist, in most cases) are recommended for patients with persistent or permanent atrial fibrillation. • Intravenous administration of β-blockers or nondihydropyridine calcium channel antagonists is recommended to slow the ventricular response to atrial fibrillation in the acute setting, exercising caution in patients with hypotension or heart failure. • Intravenous administration of digoxin or amiodarone is recommended to control the heart rate in patients with atrial fibrillation and heart failure who do not have an accessory pathway. • Digoxin is effective following oral administration to control the heart rate at rest in patients with atrial fibrillation and is indicated for patients with heart failure, LV dysfunction, or for sedentary individuals. • A combination of digoxin and either a β-blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise in patients with atrial fibrillation. The choice of medication should be individualized and the dose modulated to avoid bradycardia. • Intravenous amiodarone can be useful to control the heart rate in patients with atrial fibrillation when other measures are unsuccessful or contraindicated. • When the ventricular rate cannot be adequately controlled both at rest

Clinical Guideline	Recommendation(s)
	and during exercise in patients with atrial fibrillation using a β-blocker, nondihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control the heart rate. • Intravenous procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with atrial fibrillation involving conduction over an accessory pathway. • In patients with decompensated heart failure and atrial fibrillation, intravenous administration of a nondihydropyridine calcium channel antagonist may exacerbate hemodynamic compromise and is not recommended. • Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists to patients with atrial fibrillation and a preexcitation syndrome may paradoxically accelerate the ventricular response and is not recommended. • Amiodarone is considered a suitable alternative agent for heart rate control when conventional measures are ineffective • Dofetilide and ibutilide are effective for conversion of atrial flutter and atrial fibrillation, but are not effective for control of the ventricular rate. • Propafenone exerts mild beta-blocking effects that may slow conduction across the AV node, but this is seldom sufficient to control the rate in patients with atrial fibrillation, and AV conduction may accelerate when the atrial rhythm becomes slower and more regular, so other agents in addition to propafenone are generally required to maintain control of the heart rate when atrial fibrillation recurs. • Combinations of drugs may be required to achieve adequate rate control in some patients with atrial fibrillation, but care should be taken to avoid bradycardia. • The addition of other drugs to digoxin is commonly required to control the rate during exercise. In general, the combination of digoxin and a β-blocker appears more effective than the combination of digoxin with a calcium channel antagonist. <u>Newly Discovered Atrial Fibrillation</u> • In patients who have self-limited episodes of atrial fibrillation, antiarrhythmic drugs are usually unnecessary to prevent recurrence unless atrial fibrillation is associated with severe symptoms related to hypotension, myocardial ischemia, or heart failure. • When atrial fibrillation persists, one option is to accept progression to permanent atrial fibrillation, with attention to antithrombotic therapy and control of the ventricular rate. • The decision to attempt restoration of sinus rhythm should be based on the severity of arrhythmia-related symptoms and the potential risk of antiarrhythmic drugs. <u>Cardioversion of Atrial Fibrillation</u> • Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of atrial fibrillation. • Administration of amiodarone is a reasonable option for pharmacological cardioversion of atrial fibrillation. • A single oral bolus dose of propafenone or flecainide may be used to terminate persistent atrial fibrillation outside the hospital once treatment has proven safe in hospital for selected patients without sinus or atrioventricular (AV) node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a β-blocker or

Clinical Guideline	Recommendation(s)
	nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs. • Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent atrial fibrillation when rapid restoration of sinus rhythm is not deemed necessary. • Administration of quinidine or procainamide might be considered for pharmacological cardioversion of atrial fibrillation, but the usefulness of these agents is not well established. • Digoxin and sotalol may be harmful when used for pharmacological cardioversion of atrial fibrillation and are not recommended. • Quinidine, procainamide, disopyramide, and dofetilide should not be started out of hospital for conversion of atrial fibrillation to sinus rhythm. • Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent atrial fibrillation. • For patients with persistent atrial fibrillation, administration of β-blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of atrial fibrillation is uncertain. • Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of atrial fibrillation. • Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of atrial fibrillation in patients with certain forms of heart disease once the safety of the drug has been verified for the patient. <u>Recurrent Paroxysmal or Persistent Atrial Fibrillation</u> • In a given patient, several antiarrhythmic drugs may be effective, and the initial selection is based mainly on safety and tolerability. • Flecainide, propafenone and sotalol are recommended to maintain normal sinus rhythm in patients with no (or minimal) heart disease, because they are generally well tolerated and carry relatively little risk of toxicity. When these drugs prove ineffective or are associated with side effects, the second-line choices include amiodarone and dofetilide. Third-line agents include disopyramide, procainamide, or quinidine. • Flecainide and propafenone are recommended as initial therapy to maintain normal sinus rhythm in patients with hypertension and no evidence of left ventricular hypertrophy because they do not prolong repolarization or the QT interval. Second-line therapy includes sotalol, amiodarone and dofetilide. Disopyramide, procainamide, and quinidine are considered third-line agents. • Amiodarone is recommended to maintain normal sinus rhythm in patients with hypertension who have evidence of substantial left ventricular hypertrophy. • Dofetilide and sotalol are recommended to maintain normal sinus rhythm in patients with coronary artery disease, followed by amiodarone. • Amiodarone and dofetilide are recommended to maintain normal sinus rhythm in patients with heart failure. <u>Special Considerations</u> • Preoperative administration of amiodarone reduces the incidence of atrial fibrillation in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for

Clinical Guideline	Recommendation(s)
	postoperative atrial fibrillation. • It is reasonable to restore sinus rhythm by pharmacological cardioversion with ibutilide in patients who develop postoperative atrial fibrillation as advised for nonsurgical patients. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative atrial fibrillation, as recommended for other patients who develop atrial fibrillation. • Prophylactic administration of sotalol may be considered for patients at risk of developing atrial fibrillation following cardiac surgery. • Administration of quinidine or procainamide may be considered to achieve pharmacological cardioversion in hemodynamically stable patients who develop atrial fibrillation during pregnancy. • Antiarrhythmic medications can be useful to prevent recurrent atrial fibrillation in patients with hypertrophic cardiomyopathy. Available data is insufficient to recommend one agent over another in this situation, but disopyramide combined with a β-blocker or nondihydropyridine calcium channel antagonist or amiodarone alone is generally preferred. • In those patients with atrial fibrillation and concurrent obstructive lung disease, therapy with β-blockers, sotalol, propafenone, and adenosine are not recommended.
National Institute for Health and Clinical Excellence (NICE): **Atrial Fibrillation[20] (2006)**	• Class Ic drugs are the agents of choice for the pharmacological cardioversion of patients with persistent atrial fibrillation and no structural heart disease. • Amiodarone is the drug of choice for pharmacological cardioversion of patients with persistent atrial fibrillation and structural heart disease. • It is recommended that therapy with amiodarone or sotalol be initiated at least 4 weeks prior to cardioversion in those atrial fibrillation patients who may not be successful at restoring sinus rhythm, such as those who have failed on previous attempts. • The use of antiarrhythmics should be individualized based on the patient's comorbidities, cardiac history and potential risk for side effects. • Appropriate antithrombotic therapy should be used in patients with persistent atrial fibrillation, regardless if they are to receive rhythm control or rate control therapy. • Rhythm control is the recommended initial therapy for patients with atrial fibrillation and the following conditions: symptomatic, young, first presentation of atrial fibrillation, atrial fibrillation due to secondary causes, and/or CHF. • As long as there are no risk factors for recurrence are present, therapy with an antiarrhythmic agent is not necessary for sinus rhythm maintenance in those patients who had persistent atrial fibrillation from a secondary cause that has been corrected. • β-blockers are the recommended first-line agents, followed by amiodarone as a second-line agent, for the maintenance of sinus rhythm in those patients with persistent atrial fibrillation and structural heart disease. • β-blockers are the recommended first-line agents, followed by a Class Ic agent or sotalol as the second-line agents and amiodarone as the third line agent, for the maintenance of sinus rhythm in those patients with persistent atrial fibrillation without structural heart disease. • β-blockers or rate-limiting calcium antagonists are the recommended first-line agents for rate control in those patients with permanent atrial

Clinical Guideline	Recommendation(s)
	fibrillation. Digoxin is only recommended to be used in patients that are predominately sedentary. • In patients who have permanent atrial fibrillation and need therapy to control heart rate during normal activities in addition to the β-blockers or rate-limiting calcium antagonists, digoxin may be added. • In patients who have permanent atrial fibrillation and need therapy to control heart rate during normal activities and exercise, in addition to the β-blockers or rate-limiting calcium antagonists, digoxin may be added. • β-blockers are the recommended first-line treatment options, followed by a Class Ic antiarrhythmic agent or sotalol as a second-line agents, followed by amiodarone as a third line agent, for the treatment of symptomatic paroxysms and no structural heart disease. • β-blockers are the recommended first-line treatment option, followed sotalol as a second-line agent, followed by amiodarone as a third line agent, for the treatment of paroxysmal atrial fibrillation and coronary artery disease. • β-blockers are the recommended first-line treatment option, followed by amiodarone as a second-line agent, for the treatment of paroxysmal atrial fibrillation and poor LVEF. • Patients who are receiving medication management for the treatment of their paroxysmal atrial fibrillation should be closely monitored for side effects of therapy. • IV amiodarone should be used in patients with new onset of atrial fibrillation and non life-threatening hemodynamic instability where electrical cardioversion is delayed. • Flecainide may be used to cardiovert patients with Wolff–Parkinson–White syndrome and non life-threatening hemodynamic instability. It is recommended not to use diltiazem, verapamil, or digoxin to cardiovert these patients. • In those patients who have poorly controlled ventricular rates causing hemodynamic instability, it is recommended to use a pharmacological rate-control strategy for treatment. • IV β-blockers or rate-limiting calcium antagonists are the recommended first-line agents, followed by amiodarone as a second-line agent for urgent rate control. • Amiodarone, β-blockers, sotalol, or rate-limiting calcium channel antagonists are recommended agents to prevent postoperative atrial fibrillation in those patients undergoing cardiothoracic surgery. Digoxin is not recommended in this specific situation. • Patients receiving β-blocker therapy prior to cardiothoracic surgery should continue their therapy unless indicated otherwise. • Rhythm control is the recommend initial therapy regimen for patients following cardiothoracic unless contraindications are present. • Patients should have a follow-up visit with their health care practitioner at 1 month and 6 months post successful cardioversion to assess maintenance of sinus rhythm.
American College of Chest Physicians (ACCP): **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery**[17] **(2005)**	• β-blockers and nondihydropyridine calcium channel blockers are recommended as first and second-line agents to control ventricular response rate in atrial fibrillation after cardiac surgery. • Agents with proarrhythmic properties and those that are contraindicated in patients with coronary artery disease have not been shown to be effective in controlling the ventricular response rate in atrial fibrillation after cardiac surgery. • Amiodarone is the recommended first-line agent for pharmacologic

Clinical Guideline	Recommendation(s)
	rhythm control of postoperative atrial fibrillation or atrial flutter in patients with depressed LV function who do not need urgent electrical cardioversion. • Sotalol and Class Ia antiarrhythmics are the recommended first-line agents for pharmacologic rhythm control of postoperative atrial fibrillation or atrial flutter in patients with coronary artery disease without CHF. • When prophylaxis to prevent postoperative atrial fibrillation is indicated, β-blockers are the recommended agents. • Sotalol may be an alternative therapy to prevent postoperative atrial fibrillation, but its ability to cause toxicity may not make it a favorable option. • Amiodarone may also be considered as an alternative therapy to β-blockers to prevent postoperative atrial fibrillation, but its ability to cause toxicity may not make it a favorable option.
American Academy of Family Physicians (AAFP)/American College of Physicians (ACP): **Management of Newly Detected Atrial Fibrillation[18] (2003)**	• The recommendations provided in this guideline do not apply to the following patients: those with postoperative or post–MI atrial fibrillation, those with NYHA Class IV heart failure, those already taking antiarrhythmic drugs, or those with valvular disease. • For the treatment of atrial fibrillation, rate control (with chronic anticoagulation) is the recommended first-line treatment strategy in the majority of patients. Due to the lack of efficacy shown in clinical trials in reducing morbidity and mortality, rhythm control should be reserved for occasions when necessary, such as patient symptoms, exercise tolerance, and patient preference. • Atenolol, metoprolol, diltiazem and verapamil are the recommended agents of choice for the treatment of atrial fibrillation who require rate control at rest and during exercise. • Digoxin may be used as a second-line agent for those patients with atrial fibrillation who require rate control at rest. • Pharmacological cardioversion is an appropriate treatment option for patients who elect to undergo acute cardioversion to achieve sinus rhythm. • Agents that have been shown to be effective during pharmacological cardioversion of atrial fibrillation include ibutilide, flecainide, dofetilide, propafenone, and amiodarone. Quinidine also has some moderate evidence to support its use for pharmacological cardioversion of atrial fibrillation. Due to the lack of safety data, the AAFP/ACP have not made recommendations regarding the setting of cardioversion. • Due to the risks associated with rhythm maintenance therapy, it is not recommended to convert a majority of atrial fibrillation patients to sinus rhythm. Rhythm maintenance therapy may be appropriate during certain circumstances, including in those patients whose quality of life is affected by atrial fibrillation. The agents that are recommended for rhythm maintenance include amiodarone, disopyramide, propafenone, and sotalol. The agent should be chosen based on patient specific characteristics. • For patients with congestive systolic heart failure and LV hypertrophy, amiodarone is considered one of the safer agents recommended. • In patients with coronary artery disease, sotalol and amiodarone are considered to be the safest recommended agents.
American College of Cardiology (ACC)/American Heart Association (AHA)/European	<u>Drug Therapy for Ventricular Arrhythmias</u> • β-blockers are currently the mainstay of pharmacologic therapy for the treatment of arrhythmias, due to their safety profile and effectiveness.

Clinical Guideline	Recommendation(s)
Society of Cardiology (ESC): **Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[16] (2006)**	• Other than β-blockers, alternative antiarrhythmic agents currently available have not been proven effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death (SCD). • For patients that are arrhythmia-prone, antiarrhythmic agents may be effective as adjunctive therapy in particular situations. • Caution should be used when any antiarrhythmic agent is used for therapy, as there are many side effects associated with these agents. • β-blockers, or alternatively, amiodarone or sotalol, may be used in patients with ventricular tachycardia (VT) who do not meet criteria for an ICD. • Sotalol or, alternatively the combination of β-blockers and amiodarone, may be used in patients with ICDs who have recurrent VT/ventricular fibrillation (VF) with frequent appropriate ICD firing. <u>Ventricular Arrhythmia and Sudden Cardiac Death Related to Specific Pathology</u> • Amiodarone, often in combination with β-blockers, can be useful for patients with LVD due to prior MI and symptoms due to VT unresponsive to β-blocking agents. • Sotalol is reasonable therapy to reduce symptoms resulting from VT for patients with LVD due to prior MI unresponsive to β-blocking agents. • Alternative therapies to the ICD to improve symptoms due to frequent episodes of sustained VT or VF in patients with LVD due to prior MI include agents such as amiodarone or sotalol. • To reduce symptoms in patients due to recurrent hemodynamically stable VT with LVD due to prior MI and who cannot or refuse to have an ICD implanted, amiodarone may be used as an alternative therapy. • To improve symptoms in patients with LVD due to prior MI and recurrent hemodynamically stable VT whose left ventricular ejection fraction (LVEF) is greater than 40% and an ICD is not appropriate, amiodarone may be considered an alternative treatment option. • In patients with LVD due to prior MI where an ICD is indicated but is not appropriate or desired by the patient, amiodarone may be considered an alternative treatment option. • Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. • Class Ic antiarrhythmic agents are not recommended in patients with a past history of MI. <u>Congenital Heart Disease</u> • Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated premature ventricular contractions (PVCs). <u>Metabolic and Inflammatory Conditions</u> • Antiarrhythmic therapy can be useful in patients with symptomatic non-sustained VT or sustained VT during the acute phase of myocarditis. <u>Pericardial Disease</u> • Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of SCD in patients with pulmonary arterial hypertension or other pulmonary conditions. <u>Ventricular Arrhythmias Associated With Cardiomyopathies</u> Dilated Cardiomyopathy (DCM) (Nonischemic): • Amiodarone may be considered for sustained VT or VF in patients

Clinical Guideline	Recommendation(s)
	with nonischemic DCM. Hypertrophic Cardiomyopathy (HCM) • Amiodarone therapy can be effective for treatment in patients with HCM with a history of sustained VT and/or VF when ICD is not feasible. • Amiodarone may be considered for primary prophylaxis against SCD in patients with HCM who have one or more major risk factor for SCD, if ICD implantation is not feasible. Arrhythmogenic Right Ventricular (RV) Cardiomyopathy • Amiodarone or sotalol can be effective for treatment of sustained VT or VF in patients with arrhythmogenic RV cardiomyopathy when ICD implantation is not feasible. Heart Failure(HF) • Amiodarone, sotalol and/or other β-blockers are recommended pharmacological adjuncts to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with heart failure. • Amiodarone is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence. • Amiodarone, sotalol, and/or β-blockers may be considered as pharmacological alternatives to ICD therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with heart failure for whom ICD therapy is not feasible. Genetic Arrhythmia Syndromes: Long QT Syndrome (LQTS) • β-blockers are recommended for patients with an LQTS clinical diagnosis (i.e., in the presence of prolonged QT interval). • Implantation of an ICD along with use of β-blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year. • β-blockers can be effective to reduce SCD in patients with a molecular LQTS analysis and normal QT interval. • Implantation of an ICD with continued use of β-blockers can be effective to reduce SCD in LQTS patients experiencing syncope and/or VT while receiving β-blockers and who have reasonable expectation of survival with a good functional status for more than 1 year. Genetic Arrhythmia Syndromes: Short QT Syndrome and Brugada Syndrome • Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. Genetic Arrhythmia Syndromes: Catecholaminergic Polymorphic Ventricular Tachycardia • β-blockers are indicated for patients who are clinically diagnosed with catecholaminergic polymorphic VT on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias. • β-blockers can be effective in patients without clinical manifestations when the diagnosis of catecholaminergic polymorphic VT is established during childhood based on genetic analysis. • β-blockers may be considered for patients with catecholaminergic polymorphic VT who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. Arrhythmias in Structurally Normal Hearts

Clinical Guideline	Recommendation(s)
	Idiopathic Ventricular Tachycardia: • Drug therapy with β-blockers and/or calcium channel blockers can be useful in patients with structurally normal hearts with symptomatic VT arising from the right ventricle. <u>Ventricular Arrhythmias and Sudden Cardiac Death Related to Specific Populations</u> • In pregnant women with the LQTS who have had symptoms, it is beneficial to continue β-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. • The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients. • Digoxin or verapamil should not be used for treatment of sustained tachycardia in infants when VT has not been excluded as a potential diagnosis.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antiarrhythmic agents 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 Antiarrhythmic Agents[4-13]

Indication	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Atrial Arrhythmias								
Chronic therapy in patients at high risk of symptomatic atrial fibrillation/flutter								✔ ‖
Conversion of atrial fibrillation and atrial flutter to normal sinus rhythm			✔					
Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter) in patients with atrial fibrillation/atrial flutter of greater than one week duration who have been converted to normal sinus rhythm‡			✔					
Prevention of paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms and paroxysmal supraventricular tachycardias (PSVT) in patients without structural heart disease.					✔		✔ *	
Prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease							✔ **	
Reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation or paroxysmal or persistent atrial flutter, with a recent episode of atrial fibrillation/atrial flutter and associated cardiovascular risk factors (i.e., older than 70 years of age, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter 50 mm or more or left ventricular ejection fraction [LVEF] less than 40%), who are in sinus rhythm or who will be cardioverted				✔				

Indication	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Restore normal sinus rhythm in patients with symptomatic atrial fibrillation/flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response								✔
Ventricular Arrhythmias								
Treatment of life-threatening ventricular arrhythmias (e.g., sustained ventricular tachycardia)		✔			✔	✔	✔ *	✔
Treatment of recurrent ventricular fibrillation†	✔							
Treatment of recurrent hemodynamically unstable ventricular tachycardia†	✔							

†Because of its life-threatening side effects and the substantial management difficulties associated with its use, amiodarone is indicated only for the treatment of the life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated.
‡Because dofetilide can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic.
‖This includes patients who have had previous episodes of atrial fibrillation/flutter that were so frequent and poorly tolerated as to outweigh, in the judgment of the physician and the patient, the risks of prophylactic therapy with quinidine sulfate. The increased risk of death should specifically be considered. Quinidine sulfate should be used only after alternative measures (e.g., use of other drugs to control the ventricular rate) have been found to be inadequate.
*Immediate-release formulation.
**Sustained-release formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the antiarrhythmic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antiarrhythmic Agents[4-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Amiodarone	35-65	96	Liver	Renal (<1) Bile	26-107 days
Disopyramide	60-83	20-65	Liver	Renal (40-80) Feces (15)	4-10 hours
Dofetilide	>90	60-70	Liver	Renal (80) Feces (<10)	7.5-10 hours
Dronedarone	4-15	>98	Liver	Renal (6) Feces 84)	13-19 hours
Flecainide	70-95	40-50	Liver	Renal (81-90) Feces (4-6)	7-27 hours
Mexiletine	80-90	50-70	Liver	Renal (8-15)	6-17 hours
Propafenone	4.8-23	85-97	Liver	Renal (<1) Feces (53)	2-32 hours
Quinidine	45-100	50-90	Liver	Renal (17-50) Feces (1-3)	6-8 hours

V. Drug Interactions

Significant drug interactions with the antiarrhythmic agents are listed in Table 5.

Table 5. Significant Drug Interactions with the Antiarrhythmic Agents[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
Amiodarone, Dronedarone	1	Bepridil	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when amiodarone and bepridil are coadministered.
Amiodarone, Dronedarone	1	Chloroquine	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when such combinations are coadministered.
Amiodarone	1	Digoxin	Amiodarone may increase the oral bioavailability and decrease the systemic clearance of digoxin; additional mechanisms may exist. Mechanism of interaction is unknown but it is thought that multiple mechanisms are involved.
Amiodarone, Dronedarone	1	Dofetilide	The risk of cardiovascular toxicity, including torsades de pointes, may be increased by coadministration of dofetilide and amiodarone or dronedarone. Pharmacologic effects of dofetilide and amiodarone on electrical conduction of the heart may be additive.
Amiodarone, Disopyramide, Dronedarone,	1	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when such

Generic Name(s)	Significance Level	Interaction	Mechanism
Flecainide Propafenone, Quinidine			combinations are coadministered.
Amiodarone, Dronedarone	1	Haloperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when such combinations are coadministered.
Amiodarone	1	HMG-CoA reductase inhibitors	Amiodarone may inhibit the metabolism of HMG-CoA reductase inhibitors (CYP3A4) thereby increasing plasma concentrations and increasing the risk of toxicity.
Amiodarone, Dronedarone	1	Maprotiline	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when such combinations are coadministered.
Amiodarone, Dofetilide, Dronedarone, Flecainide, Propafenone,	1	Methadone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when such combinations are coadministered.
Amiodarone, Disopyramide, Dofetilide, Dronedarone, Flecainide, Propafenone, Quinidine	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and certain antiarrhythmics. The black box warning contained in the official package labeling for nilotinib states that use of nilotinib with medications that prolong the QT interval should be avoided.
Amiodarone, Dronedarone	1	Pentamidine	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when amiodarone or dronedarone is coadministered with pentamidine.
Amiodarone, Disopyramide, Dofetilide, Dronedarone, Quinidine	1	Phenothiazines	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Amiodarone, Dronedarone, Quinidine	1	Phosphodiesterase Type 5 inhibitors	Phosphodiesterase type 5 inhibitors and certain antiarrhythmics may cause additive adverse effects when coadministered. Prolonged QT interval with the potential for cardiac arrhythmias may occur.
Amiodarone, Disopyramide, Dronedarone, Flecainide, Propafenone, Quinidine	1	Pimozide	Certain antiarrhythmics and pimozide may cause additive adverse effects when coadministered. Cardiovascular toxicity, including torsades de pointes, may occur due to additive
Amiodarone, Dronedarone, Flecainide, Propafenone,	1	Protease inhibitors	Protease inhibitors may inhibit the metabolism (CYP3A4) of amiodarone thereby increasing amiodarone concentrations and increasing the risk of

Generic Name(s)	Significance Level	Interaction	Mechanism
			amiodarone toxicity.
Amiodarone	1	Quinidine	Mechanism of interaction is unknown. Concurrent therapy may lead to an increase in quinidine concentrations and produce potentially fatal cardiac dysrhythmias.
Amiodarone, Disopyramide, Dofetilide, Dronedarone, Flecainide, Propafenone, Quinidine	1	Quinolones	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Amiodarone, Dronedarone,	1	Serotonin Receptor Antagonist Antiemetics	The risk of QT-interval prolongation and cardiac arrhythmias caused by serotonin receptor antagonist antiemetics may be increased by coadministration of amiodarone/dronedarone.
Amiodarone, Dronedarone	1	Tyrosine kinase receptor inhibitors	Additive QT interval prolongation is listed in the manufacturer's package labeling for tyrosine kinase receptor inhibitors as a possibility when coadministered with amiodarone/dronedarone. Clinical impact is not known. QT interval effects of each agent may be additive. Other mechanisms may exist.
Amiodarone	1	Warfarin	Amiodarone inhibits the metabolism (CYP1A2 and CYP2C9) of the R- and S-enantiomers of warfarin; therefore the hypoprothrombinemic effects may be augmented.
Amiodarone, Dronedarone	1	Ziprasidone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when amiodarone/dronedarone and ziprasidone are coadministered.
Disopyramide, Dofetilide, Dronedarone Propafenone	1	Macrolide and related antibiotics	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Dofetilide, Quinidine	1	Azole antifungals	Certain azole antifungal agents may inhibit the metabolism (CYP3A4) and active renal secretion of dofetilide or quinidine. Plasma dofetilide or quinidine concentrations may be elevated, increasing the risk of serious cardiovascular events.
Dofetilide	1	Cimetidine	Cimetidine may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular

Generic Name(s)	Significance Level	Interaction	Mechanism
			arrhythmias, including torsades de pointes.
Dofetilide	1	Progestins	Progestins may increase the pharmacologic effects and plasma concentrations of dofetilide by inhibiting the renal cation transport system.
Dofetilide	1	Thiazide diuretics	Thiazide diuretics may increase potassium excretion causing hypokalemia which may increase the risk of torsades de pointes.
Dofetilide	1	Trimethoprim	Trimethoprim may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	1	Verapamil	Verapamil may increase the rate of dofetilide absorption by increasing portal blood flow thereby increasing dofetilide plasma concentrations which may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dronedarone	1	Lithium	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when lithium is coadministered with dronedarone.
Dronedarone	1	Nefazodone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Inhibition of CYP 3A by nefazodone may decrease the metabolic elimination of dronedarone.
Dronedarone	1	Paliperidone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when paliperidone is coadministered with dronedarone.
Dronedarone	1	Propafenone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when paliperidone is coadministered with dronedarone.
Dronedarone	1	Sotalol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when dronedarone and sotalol are coadministered.
Propafenone	1	Dronedarone	Prolongation of the QT interval with

Generic Name(s)	Significance Level	Interaction	Mechanism
			possible development of cardiac arrhythmias, including torsades de pointes, should be considered when dronedarone is coadministered with propafenone.
Quinidine	1	Antiarrhythmics (Class III)	Quinidine and Class III antiarrhythmics may cause additive pharmacologic and adverse cardiovascular effects when co-administered.
Quinidine	1	Digoxin	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Quinidine	1	Protease inhibitors	Protease inhibitors may inhibit the metabolism (CYP3A4) of quinidine. Large increases in serum quinidine concentrations may occur, increasing the risk of quinidine toxicity.
Quinidine	1	Verapamil	Verapamil may decrease the clearance of quinidine and prolong its half-life which may lead to hypotension, bradycardia, ventricular tachycardia and atrioventricular block.
Quinidine	1	Warfarin	Quinine derivatives also may inhibit the hepatically synthesized clotting factors. Anticoagulation may be potentiated by quinine derivatives and hemorrhage may occur.
Amiodarone	2	Cyclosporine	Mechanism of the interaction is unknown. Amiodarone may inhibit the metabolism of cyclosporine which may lead to an increase in cyclosporine blood concentrations, possibly increasing the risk of nephrotoxicity.
Amiodarone	2	Flecainide	Amiodarone may decrease the metabolism of flecainide and plasma levels may be increased.
Amiodarone, Disopyramide, Dronedarone, Mexiletine, Quinidine	2	Hydantoins	Phenytoin may increase the hepatic metabolism of certain antiarrhythmics via stimulation of microsomal enzymes.
Amiodarone	2	Quinazolines	Plasma concentrations and pharmacologic effects of quinazolines may be increased by amiodarone due to inhibition of CYP 3A4 isoenzymes by amiodarone.
Dronedarone	2	Barbiturates	Plasma concentrations and pharmacologic effects of dronedarone may be decreased by barbiturates due to induction of CYP 3A isoenzymes by barbiturates.
Dronedarone	2	Carbamazepine	Plasma concentrations and pharmacologic effects of dronedarone may be decreased by Carbamazepine

Generic Name(s)	Significance Level	Interaction	Mechanism
			due to induction of CYP 3A isoenzymes by carbamazepine.
Dronedarone, Quinidine	2	Digoxin	Plasma concentrations and pharmacologic effects of digoxin may be increased by dronedarone or quinidine, due to inhibition of P-glycoprotein (P-gP) efflux transport.
Dronedarone	2	Diltiazem	Plasma concentrations and pharmacologic effects of dronedarone may be increased by diltiazem. Dronedarone may also increase the plasma concentrations and pharmacologic effects of diltiazem. Additionally, diltiazem may enhance the electrophysiologic effects of dronedarone. Inhibition of CYP3A isoenzymes by diltiazem may decrease the metabolic elimination of dronedarone. Likewise, inhibition of CYP3A isoenzymes by dronedarone may decrease the metabolic elimination of diltiazem.
Dronedarone	2	HMG-CoA reductase inhibitors	Plasma concentrations and pharmacologic effects of statins may be increased by dronedarone, due to inhibition of CYP3A isoenzymes and P-glycoprotein Toxicity, characterized by muscle injury may occur.
Dronedarone, Mexiletine, Propafenone, Quinidine	2	Rifamycins	Rifamycins may induce the hepatic microsomal enzymes responsible for metabolizing certain antiarrhythmics, whose increased clearance may lead to a decrease in plasma levels and a possible loss of therapeutic effects.
Dronedarone, Quinidine	2	Verapamil	Plasma concentrations and pharmacologic effects of dronedarone may be increased by verapamil. Dronedarone may also increase the plasma concentrations and pharmacologic effects of verapamil. Additionally, verapamil may enhance the electrophysiologic effects of dronedarone. Inhibition of CYP3A isoenzymes by verapamil may decrease the metabolic elimination of dronedarone. Likewise, inhibition of CYP3A isoenzymes by dronedarone may decrease the metabolic elimination of verapamil.
Flecainide, Propafenone	2	SNRIs	Plasma concentrations of flecainide and propafenone may be increased by SNRIs, due to inhibition of cytochrome CYP2D6 isoenzymes.
Mexiletine	2	Lidocaine	Plasma concentrations and pharmacologic effects of lidocaine may be increased by mexiletine. Lidocaine-

Generic Name(s)	Significance Level	Interaction	Mechanism
			related toxicity may occur. The mechanism is unknown, although displacement of lidocaine from tissue binding sites by mexiletine has been implicated in increasing plasma concentrations of lidocaine.
Mexiletine	2	Theophylline	Mexiletine may impair hepatic elimination and increase plasma concentrations of theophylline. Additive arrhythmogenic effects may also occur.
Propafenone	2	Digoxin	Propafenone may increase the pharmacologic effects of digoxin. Elevated digoxin serum concentrations occur with potential toxicity characterized by GI and neuropsychiatric symptoms. Cardiac arrhythmias may result. The mechanism is unknown.
Propafenone	2	Warfarin	The hypoprothrombinemic effect of warfarin may be increased by propafenone. The mechanism is unknown, but decreased hepatic metabolism of warfarin by propafenone is a possibility.
Quinidine	2	Aripiprazole	Quinidine may inhibit the hepatic metabolism (CYP2D6) of aripiprazole thereby increasing plasma concentrations and potentiating the pharmacologic effects and adverse reactions.
Quinidine	2	Barbiturates	Barbiturates may increase the metabolic clearance of quinidine thereby decreasing quinidine serum concentrations and elimination half-life.
Quinidine	2	β-blockers	Quinidine may inhibit the oxidative metabolism of certain β-blockers. The effects of certain β-blockers may be increased in “extensive metabolizers.”
Quinidine	2	Cimetidine	Inhibition of hepatic microsomal enzymes by cimetidine may decrease the metabolic elimination of quinidine. Additional mechanisms may exist including a decrease in renal clearance of quinidine possibly due to competition with cimetidine for renal tubular secretion.
Quinidine	2	Codeine	Quinidine may decrease pharmacologic effects of codeine, due to inhibition of CYP2D6 isoenzymes and thereby decreased metabolic conversion of codeine to morphine. Loss of analgesic effect may occur.
Quinidine	2	Nifedipine	Plasma concentrations and pharmacologic effects of quinidine may be decreased by nifedipine. Plasma concentrations and pharmacologic

Generic Name(s)	Significance Level	Interaction	Mechanism
			effects of nifedipine may be increased by quinidine, which may decrease the first-pass metabolism of nifedipine by inhibiting aromatization.
Quinidine	2	Non-depolarizing muscle relaxants	Concurrent use of these agents may cause synergistic pharmacologic effects. Non-depolarizing muscle relaxants effects may be enhanced by quinine and quinine derivatives.
Quinidine	2	Succinylcholine	Quinidine may produce a decrease in plasma cholinesterase activity resulting in a slowed metabolic rate for succinylcholine. The neuromuscular blockade produced by succinylcholine may be prolonged.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the antiarrhythmic agents are listed in Table 6. The boxed warnings for the antiarrhythmic agents are listed in Tables 7-14.

Table 6. Adverse Drug Events (%) Reported with the Antiarrhythmic Agents[4-13]

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Cardiovascular								
Alters pacing threshold	-	-	-	-	<1	-	-	-
Angina	-	-	-	-	<1	2	2-5	6
Arrhythmia	1-10	-	-	-	-	-	-	1-10
Asystole	1-10	-	-	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	-	1	-
AV block	5	<1	0.4-1.5	-	<1	<1	1-3	-
AV dissociation	-	-	-	-	-	-	<1	-
Bradycardia	3-5	-	-	3	<1	-	1-2	<1
Bundle branch block	-	-	<2	-	-	-	0-1	-
Cardiac arrest	1-10	-	<2	-	-	-	<1	-
Cardiogenic shock	1-10	-	-	-	-	<1	-	-
Chest pain	-	1-10	10	-	5	3-8	1-2	-
Conduction abnormalities	1-10	1-10	-	-	-	-	0-1	-
Congestive heart failure	-	1-10	-	-	-	-	-	-
Edema	1-10	1-10	-	✔	3.5	-	0-1	-
Electromechanical dissociation	1-10	-	-	-	-	-	-	-
Heart block	-	-	<2	-	<1	-	-	<1
Hypertension	-	-	-	-	-	-	0-1	-
Hypotension	<1	1-10	-	-	-	<1	-	✔
Myocardial infarction	-	-	<2	-	-	-	-	-
Palpitations	-	-	-	-	6	4-8	1-3	7
Premature ventricular contractions	-	-	-	-	-	1-2	1-2	-
Proarrhythmia	<1	<1	-	-	4-12	10-15	2-10	-
P-R increased	-	-	-	-	<1	-	-	-
QRS duration	-	-	-	-	<1	-	1-2	-
QT interval increased	<1	-	-	-	-	-	-	>10
QTc prolonged	-	-	-	28	-	-	-	-
SA node dysfunction	1-3	-	-	-	-	-	-	-
Sinus arrest	<1	-	-	-	-	<1	-	-
Sinus node dysfunction	-	-	-	-	1.2	-	<1	-
Stroke	-	-	<2	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Tachycardia	-	-	-	-	1-3	-	-	<1
Torsades de pointes	<1	-	0.9-10.5	-	-	<1	-	<1
Ventricular arrhythmia	-	-	-	-	<1	-	-	-
Ventricular fibrillation	<1	-	0-0.4	-	-	-	-	<1
Ventricular rate increase	-	-	-	-	<1	-	-	<1
Ventricular tachycardia	1-10	-	2.6-3.7	-	-	-	1-3	<1
Central Nervous System								
Abnormal gait/ataxia	3-40	-	-	-	-	-	-	-
Amnesia	-	-	-	-	<1	-	<1	-
Anxiety	-	-	-	-	1-3	-	1-2	-
Ataxia	-	-	-	-	1-3	10-20	0-2	-
Cerebral hypoperfusion	-	-	-	-	-	-	-	<1
Coma	-	-	-	-	-	-	<1	-
Confusion	<1	-	-	-	-	1-10	<1	<1
Delirium	-	-	-	-	-	-	-	<1
Depersonalization	-	-	-	-	<1	-	-	-
Depression	-	<1	-	-	1-3	2	<1	<1
Disorientation	<1	-	-	-	-	-	-	-
Dizziness	3-40	1-10	8	-	19-30	20-25	4-15	-
Drowsiness	-	-	-	-	-	-	1	-
Encephalopathy	<1	-	-	-	-	-	-	-
Euphoria	-	-	-	-	<1	-	-	-
Fatigue	3-40	1-10	-	-	8	-	2-6	7
Fever	-	-	-	-	1-3	-	-	<1
Flushing	-	-	-	-	-	-	-	<1
Hallucinations	<1	-	-	-	-	<1	-	<1
Headache	3-40	1-10	11	-	4-10	1-10	2-5	7
Impaired memory	3-40	-	-	-	-	-	-	-
Insomnia	3-40	<1	4	-	1-3	5-7	0-2	-
Involuntary movement	3-40	-	-	-	-	-	-	-
Lightheadedness	-	-	-	-	-	11-25	-	15
Malaise	3-40	1-10	-	-	1-3	-	-	-
Memory loss	-	-	-	-	-	-	<1	-
Nervousness	-	1-10	-	-	5	5-10	-	2
Paresis	-	-	-	-	1-3	-	-	-
Peripheral neuropathy	3-40	-	-	-	-	-	-	-
Poor coordination	3-40	-	-	-	-	10	-	1

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Psychotic reaction/psychosis	-	<1	-	-	-	<1	<1	<1
Seizure	-	-	-	-	-	<1	0.3	-
Sleep disturbances	3-40	-	-	-	-	-	-	3
Somnolence	-	-	-	-	1-3	-	-	-
Syncope	-	1-10	<2	-	1-10	<1	1-2	1-8
Tardive dyskinesia	-	-	-	-	<1	-	-	-
Vertigo	-	-	-	-	1-3	-	<1	<1
Visual disturbances	<10	-	-	-	16	-	-	<1
Dermatological								
Abnormal pigmentation	-	-	-	-	-	-	-	<1
Allergic dermatitis	-	-	-	≤5	-	-	-	-
Alopecia	<1	-	-	-	<1	<1	<1	-
Eczematous dermatitis	-	-	-	≤5	-	-	-	<1
Epididymitis	<1	-	-	-	-	-	-	-
Erythema multiforme	<1	-	-	-	-	-	-	-
Exfoliative dermatitis	<1	-	-	-	<1	<1	-	<1
Flushing	1-10	-	-	-	-	-	-	-
Generalized dermatoses	-	1-10	-	-	-	-	-	-
Leukocytoclastic vasculitis	<1	-	-	-	-	-	-	-
Lichen planus	-	-	-	-	-	-	-	<1
Livedo reticularis	-	-	-	-	-	-	-	<1
Melanin pigmentation of hard palate	-	-	-	-	-	-	-	<1
Phlebitis	1-10	-	-	-	-	-	-	-
Photophobia	<1	-	-	-	<1	-	-	-
Photosensitivity	10-75	-	-	<1	-	-	-	<1
Pruritus	<1	1-10	-	≤5	<1	-	<1	<1
Purpura	-	-	-	-	-	-	<1	-
Rash	<1	1-10	3	≤5	1-3	4	1-3	5
Slate blue skin discoloration	<10	-	-	-	-	-	-	-
Spontaneous ecchymosis	<1	-	-	-	-	-	-	-
Stevens-Johnson syndrome	<1	-	-	-	-	<1	-	-
Toxic cutaneous blisters	-	<1	-	-	-	-	-	-
Toxic epidermal necrolysis	<1	-	-	-	-	-	-	-
Urticaria	-	-	-	-	<1	<1	-	<1
Vasculitis	<1	-	-	-	-	-	-	-
Endocrine and Metabolic								
Decreased libido	1-10	-	-	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Erectile dysfunction	<1	-	-	-	-	-	-	-
Gynecomastia	-	<1	-	-	-	-	-	-
Hyperthyroidism	3-10	-	-	-	-	-	-	-
Hypothyroidism	1-22	-	-	-	-	-	-	-
Impotence	<1	1-3	-	-	-	<1	<1	-
Gastrointestinal								
Abdominal bloating	-	1-10	-	-	-	-	-	-
Abdominal distention	-	1-10	-	-	-	-	-	-
Abdominal pain	1-10	-	3	4	3	1	1-2	-
Abnormal salivation	1-10	-	-	-	-	-	-	-
Abnormal taste	1-10	-	-	-	<1	-	3-23	>10
Angioedema	<1	-	<2	-	-	-	-	<1
Anorexia	10-33	1-10	-	-	1-3	-	1-2	>10
Cholestasis	-	-	-	-	-	-	0.1	-
Constipation	10-33	11	-	-	1	4-5	2-7	-
Diarrhea	-	1-10	3	9	0.7-3	4-5	1-3	35
Dry throat	-	1-10	-	-	-	-	-	-
Dysgeusia	-	-	-	<1	-	-	-	-
Dyspepsia	-	-	-	2	-	-	1-3	-
Dysphagia	-	-	-	-	-	<1	-	-
Esophagitis	-	-	-	-	-	-	-	<1
Flatulence	-	1-10	-	-	-	-	0-1	-
Gastrointestinal distress	-	-	-	-	-	41	-	>10
Nausea	10-33	1-10	5	5	9	40	2-11	>10
Stomach cramping	-	-	-	-	-	-	-	22
Swollen lips/tongue/mouth	-	-	-	-	<1	-	-	-
Upper gastrointestinal bleeding	-	-	-	-	-	<1	-	-
Vomiting	10-33	1-10	-	2	-	40	2-11	>10
Weight gain	-	1-10	-	-	-	-	-	-
Xerostomia	-	32	-	-	-	3	1-2	-
Genitourinary								
Dysuria	-	<1	-	-	-	-	-	-
Urinary frequency	-	1-10	-	-	-	-	-	-
Urinary hesitancy	-	14-23	-	-	-	-	-	-
Urinary retention	-	1-10	-	-	<1	<1	-	-
Urinary urgency	-	1-10	-	-	-	-	-	-
Hematological								

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Agranulocytosis	<1	<1	-	-	-	<1	<1	-
Aplastic anemia	<1	-	-	-	-	-	-	-
Coagulation abnormalities	1-10	-	-	-	-	-	-	-
Granulocytopenia	-	-	-	-	<1	-	<1	-
Hemolytic anemia	<1	-	-	-	-	-	-	<1
Hemoptysis	<1	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	<1	<1	<1	-
Neutropenia	<1	-	-	-	-	-	-	-
Pancytopenia	<1	-	-	-	-	-	-	<1
Thrombocytopenia	<1	<1	-	-	<1	<1	<1	<1
Hepatic								
AST or ALT level >2x normal	15-50	<1	-	-	-	-	-	-
Cirrhosis	<3	-	-	-	-	-	-	-
Hepatic necrosis	-	-	-	-	-	<1	-	-
Hepatitis	<3	-	-	-	-	<1	0.03	<1
Hepatotoxicity	-	<1	<2	-	-	-	-	<1
Laboratory Test Abnormalities								
Hypercholesterolemia	-	1-10	-	-	-	-	-	-
Hyperglycemia	<1	-	-	-	-	-	<1	-
Hypertriglyceridemia	<1	1-10	-	-	-	-	-	-
Hypoglycemia	-	<1	-	-	-	-	-	-
Hypokalemia	-	1-10	-	✔	-	-	-	-
Hypomagnesemia	-	-	-	✔	-	-	-	-
Serum creatinine increased	-	<1	-	51	-	-	-	-
Musculoskeletal								
Arthralgia	-	-	-	-	-	1	0-1	<1
Back pain	-	-	3	-	-	-	-	-
Facial paralysis	-	-	<2	-	-	-	-	-
Flaccid paralysis	-	-	<1	-	-	-	-	-
Lupus	-	<1	-	-	-	<1	<1	-
Lupus-like syndrome	-	-	-	-	-	-	-	<1
Muscle pain (myalgia)	-	1-10	-	-	-	-	-	<1
Myopathy	<1	-	-	-	-	-	-	-
Neuropathy	-	<1	-	-	<1	2-4	<1	-
Paralysis	-	-	<2	-	-	-	-	-
Paresthesia	-	<1	<2	-	1	2	<1	-
Parkinsonian symptoms	<1	-	-	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Rhabdomyolysis	<1	-	-	-	-	-	-	-
Trembling	-	-	-	-	-	>10	-	-
Tremor	3-40	-	-	-	5	13	0-1	2
Unsteady gait	-	-	-	-	-	>10	-	-
Weakness	<1	1-10	-	7	5	5	1-2	5
Ocular								
Blurred vision	-	1-10	-	-	1-10	5-7	1-6	1-10
Corneal micro-deposits	>90	-	-	-	<1	-	-	-
Diplopia	-	-	-	-	1-3	-	-	-
Dry eyes	-	1-10	-	-	-	-	-	-
Halo vision	<5	-	-	-	-	-	-	-
Mydriasis	-	-	-	-	-	-	-	<1
Nystagmus	-	-	-	-	-	6	-	-
Optic neuritis	1	-	-	-	-	-	-	<1
Optic neuropathy	<1	-	-	-	-	-	-	-
Uveitis	-	-	-	-	-	-	-	<1
Visual disturbances	2-9	-	-	-	-	-	-	-
Renal								
Acute renal failure	<1	-	-	-	-	-	<1	-
Nephropathy	-	-	-	-	-	-	-	<1
Nephrotic syndrome	-	-	-	-	-	-	<1	-
Respiratory								
Acute respiratory distress syndrome	2	-	-	-	-	-	-	-
Alveolar pneumonitis	✔	-	-	-	-	-	-	-
Apnea	-	-	-	-	-	-	<1	-
Bronchiolitis obliterans organizing pneumonia	<1	-	-	-	-	-	-	-
Bronchospasm	<1	-	-	-	<1	-	-	<1
Dyspnea	<1	1-10	6	-	~10	3	2-5	-
Hypersensitivity pneumonitis	✔	-	-	-	-	-	-	-
Pleuritis	<1	-	-	-	-	-	-	-
Pneumonitis	✔	-	-	-	<1	-	-	<1
Pulmonary alveolar hemorrhage	<1	-	-	-	-	-	-	-
Pulmonary edema	<1	-	-	-	-	-	-	-
Pulmonary fibrosis	✔	-	-	-	-	<1	-	-
Pulmonary inflammation	✔	-	-	-	-	-	-	-
Pulmonary mass	<1	-	-	-	-	-	-	-
Pulmonary toxicity	2-17	-	-	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Respiratory failure	<1	<1	-	-	-	-	-	<1
Respiratory tract infection	-	-	7	-	-	-	-	-
Wheezing	<1	-	-	-	-	-	-	1-10
Other								
Abnormal smell	1-10	-	-	-	-	-	-	-
Anaphylactic shock	<1	-	-	-	-	-	-	-
Blood urea nitrogen increased	-	<1	-	-	-	-	-	-
Bone marrow granuloma	<1	-	-	-	-	-	-	-
Cholestatic jaundice	-	<1	-	-	-	-	-	-
Cinchonism	-	-	-	-	-	-	-	<1
Diaphoresis	-	-	-	-	-	-	1	-
Flu syndrome	-	-	4	-	-	-	-	-
Hearing impairment	-	-	-	-	-	-	-	<1
Hypoxia	<1	-	-	-	-	-	-	-
Increased bleeding time	-	-	-	-	-	-	<1	-
Increased creatine phosphokinase	-	-	-	-	-	-	-	<1
Lymphadenopathy	-	-	-	-	-	-	-	<1
Myelofibrosis	-	-	-	-	-	<1	-	-
Pancreatitis	<1	-	-	-	-	<1	-	-
Pseudotumor cerebri	<1	-	-	-	-	-	-	-
Sicca syndrome	-	-	-	-	-	-	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	<1	-	-	-	-	-	<1	-
Thyroid cancer/nodules	<1	-	-	-	-	-	-	-
Thyrotoxicosis	<1	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	1-3	2-3	<1	1-10
Vascular collapse	-	-	-	-	-	-	-	<1
Vasculitis	-	-	-	-	-	-	-	<1

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Amiodarone

WARNING
Life-threatening arrhythmias: Amiodarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity. **Potentially fatal toxicities:** Amiodarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10% to 17% in some series of patients with ventricular arrhythmias given doses of approximately 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal approximately 10% of the time. Liver injury is common with amiodarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, amiodarone can exacerbate the arrhythmia (e.g., by making the arrhythmia less well tolerated or more difficult to reverse). This has occurred in 2% to 5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2% to 5%. In most cases, all of these events should be manageable in the proper clinical setting. Although the frequency of such proarrhythmic events does not appear greater with amiodarone than with many other agents used in this population, the effects are prolonged when they occur. **High-risk patients:** Even in patients at high risk of arrhythmic death in whom the toxicity of amiodarone is an acceptable risk, amiodarone poses major management problems that could be life-threatening in a population at risk of sudden death; therefore, make every effort to utilize alternative agents first. The difficulty of using amiodarone effectively and safely poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone is given, and a response generally requires at least 1 week, usually 2 weeks or more. Because absorption and elimination are variable, maintenance dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 patients required dose reduction and 18 required at least temporary discontinuation because of adverse reactions, and several series have reported 15% to 20% overall frequencies of discontinuation because of adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when amiodarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when amiodarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

Table 8. Boxed Warning for Disopyramide

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an MI more than 6 days but less than 2 years previously, an excessive mortality or nonfatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent MI) is uncertain. Considering the known proarrhythmic properties of disopyramide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of disopyramide as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Table 9. Boxed Warning for Dofetilide

WARNING
To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see Administration and Dosage. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.

Table 10. Boxed Warning for Dronedarone

WARNING
Dronedarone is contraindicated in patients with New York Heart Association (NYHA) class IV heart failure or NYHA class II to III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic. In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA study), patients given dronedarone had a greater than 2-fold increase in mortality. Do not give such patients dronedarone.

Table 11. Boxed Warning for Flecainide

WARNING
Mortality: Flecainide was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an MI more than 6 days but less than 2 years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with flecainide compared with that seen in patients assigned to a carefully matched placebo-treated group. This rate was 5.1% for flecainide and 2.3% for the matched placebo. The average duration of treatment with flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent MI) is uncertain, but at present, it is prudent to consider the risks of Class Ic agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs. **Ventricular proarrhythmic effects in patients with atrial fibrillation/flutter:** A review of the world literature revealed reports of 568 patients treated with oral flecainide for paroxysmal atrial fibrillation/flutter (PAF). Ventricular tachycardia was experienced in 0.4% of these patients. Of 19 patients in the literature with chronic atrial fibrillation (CAF), 10.5% experienced ventricular tachycardia (VT) or ventricular fibrillation (VF). Flecainide is not recommended for use in patients with CAF. Case reports of ventricular proarrhythmic effects in patients treated with flecainide for atrial fibrillation/flutter have included increased premature ventricular contractions (PVCs), VT, VF, and death. As with other Class I agents, patients treated with flecainide for atrial flutter have been reported with 1:1 atrioventricular conduction due to slowing the atrial rate. A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive flecainide. Concomitant negative chronotropic therapy such as digoxin or β-blockers may lower the risk of this complication.

Table 12. Boxed Warning for Mexiletine

WARNING
Mortality: In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an excessive mortality or non-fatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared with that seen in patients assigned to carefully matched placebo-treated groups (3.0%). The average duration of treatment with encainide or flecainide in this study was ten months. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of Mexiletine and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of Mexiletine as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmia. **Acute Liver Injury:** In postmarketing experience abnormal liver function tests have been reported, some in the first few weeks of therapy with Mexiletine hydrochloride. Most of these have been observed in the setting of congestive heart failure or ischemia and their relationship to Mexiletine hydrochloride has not been established.

Table 13. Boxed Warning for Propafenone

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an MI more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared with that seen in patients assigned to placebo (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent MI) or other antiarrhythmic drugs is uncertain, but at present, it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with nonlife-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening symptoms or signs.

Table 14. Boxed Warning for Quinidine

WARNING
Many trials of antiarrhythmic therapy for non-life threatening arrhythmias, has resulted in increased mortality; the risk of active therapy is probably greatest in patients with structural heart disease. In the case of quinidine used to prevent or defer recurrence of atrial flutter/fibrillation, meta-analysis data has shown that the mortality associated with the use of quinidine was more than three times greater than placebo. Another meta-analysis showed that in patients with various non-life-threatening ventricular arrhythmias, the mortality associated with the use of quinidine was consistently greater than that associated with the use of any of a variety of alternative antiarrhythmics.

VII. Dosing and Administration

The usual dosing regimens for the antiarrhythmic agents are listed in Table 15.

Table 15. Usual Dosing Regimens for the Antiarrhythmic Agents[4-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amiodarone	Ventricular Arrhythmias: Tablet: Initial: 800–1,600 mg daily for 1–3 weeks, then 600–800 mg daily for one month Maintenance: 400 mg daily, up to 600 mg daily, given as a single dose or divided twice daily. Intravenous (IV): Initial: 15 mg/min for 10 min (150 mg), then 1 mg/min IV for 6 hours (360 mg), then 0.5 mg/min IV for 18 hours (540 mg). Maintenance: 0.5 mg/min IV after the first 24 hours (720 mg/24 hours) with a concentration of 1-6 mg/mL Breakthrough: breakthrough ventricular fibrillation (VF)/ventricular tachycardia (VT), 150 mg IV over 10 min. When converting from IV to oral: <1 week: IV to oral 800–1,600 mg daily; 1 to 3 week: IV to oral 600–800 mg daily; >3 week: IV to oral 400 to mg daily	Safety and efficacy in pediatrics have not been established.	Tablet: 100 mg 200 mg 400 mg Injection: 50 mg/ml 150 mg/3 ml
Disopyramide	Ventricular Arrhythmias: Rapid Control (IR): Patients >50 kg: 300 mg followed by appropriate maintenance dose Patients <50 kg: 200 mg followed by appropriate maintenance dose Sustained-release formulation is not recommended for initial therapy. Maintenance: Patients >50 kg: 400–800 mg daily (divided every 6 hours	Safety and efficacy in pediatrics have not been established.	Capsule (IR): 100 mg 150 mg Capsule (SR): 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	for immediate-release or every 12 hours for sustained-release formulation). Patients <50 kg: 400 mg daily in divided doses Maximum dose: 1,200–1,600 mg daily When converting a patient from procainamide or quinine sulfate, disopyramide should be started using the regular maintenance schedule without a loading dose 6-12 hours after the last dose of quinidine sulfate or 3-6 hours after the last dose of procainamide.		
Dofetilide	Atrial fibrillation/Atrial Flutter: Normal renal function and QTc ≤440 msec: Initial: 500 mcg twice daily; at 2–3 hours after first dose, if QTc increases >15% or >500 msec, reduce dose to 250 mcg twice daily When converting a patient from a Class I or Class III antiarrhythmic agent to dofetilide, the previous antiarrhythmic agent should be discontinued for at least 3 half-lives prior to the initiation of dofetilide. When switching from amiodarone, amiodarone plasma levels should be <0.3 mcg/mL prior to initiation of dofetilide therapy.	Safety and efficacy in pediatrics have not been established.	Capsule: 125 mcg 250 mcg 500 mcg
Dronedarone	Atrial Fibrillation/Atrial Flutter: 400 mg twice a day	Safety and efficacy in pediatrics have not been established.	Tablet: 400 mg
Flecainide	Paroxysmal Atrial Fibrillation/Atrial Flutter: Initial: 50 mg every 12 hours Titration: increase by 50 mg twice daily every 4 days Maximum dose: 300 mg daily Paroxysmal Supraventricular Tachycardia: Initial: 50 mg every 12 hours Titration: increase by 50 mg twice daily every 4 days Maximum dose: 300 mg daily	Paroxysmal Atrial Fibrillation/Atrial Flutter: <6 months: Initial: 50 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily >6 months: Initial: 100 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily	Tablet: 50 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Ventricular Arrhythmias: Initial: 100 mg every 12 hours Titration: increase by 50 mg twice daily every 4 days Maximum dose: 400 mg daily When converting a patient from another antiarrhythmic agent, the previous antiarrhythmic agent should be discontinued at least 2-4 plasma half-lives prior to the initiation of flecainide therapy. When giving flecainide concurrently with amiodarone, the flecainide dose should be dropped by 50% and patient should be monitored closely for any adverse effects.	Paroxysmal Supraventricular Tachycardia: <6 months: Initial: 50 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily >6 months: Initial: 100 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily Ventricular Arrhythmia: <6 months: Initial: 50 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily >6 months: Initial: 100 mg/m^2 in 2-3 divided doses Maximum dose: 200 mg/m^2 daily	
Mexiletine	Ventricular Arrhythmias: Rapid Control: loading dose of 400 mg, then 200 mg in 8 hours Initial: 200 mg every 8 hours Titration: increase by 50–100 mg every 2-3 days or longer Maintenance: 200–400 mg every 8 hours Maximum dose: 1,200 mg daily When converting a patient from a Class I antiarrhythmic agent to mexiletine, the following titration schedule is recommended: initiated mexiletine with a 200 mg dose, and titrate to response 6-12 hours after the last dose of quinidine sulfate, 3-6 hours after the last dose of procainamide, 6-12 hours after the last dose of disopyramide or 8-12 hours after the last dose of tocainide. When switching therapy from	Safety and efficacy in pediatrics have not been established.	Capsule: 150 mg 200 mg 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	lidocaine, the lidocaine infusion should be stopped when the first oral dose of mexiletine is administered.		
Propafenone	Atrial Fibrillation/Atrial Flutter: Tablet: Initial: 150 mg every 8 hours Titration: increase every 3–4 days to 225–300 mg every 8 hours Capsule (SR): Initial: 225 mg every 12 hours Titration: increase every 5 days to 325–425 mg every 12 hours Paroxysmal Supraventricular Tachycardia: Tablet: Initial: 150 mg every 8 hours Titration: increase every 3–4 days to 225–300 mg every 8 hours Ventricular Arrhythmias: Tablet: Initial: 150 mg every 8 hours Titration: increase every 3–4 days to 225–300 mg every 8 hours	Safety and efficacy in pediatrics have not been established.	Tablet: 150 mg 225 mg 300 mg Capsule (SR): 225 mg 325 mg 425 mg
Quinidine gluconate	Atrial Fibrillation/Atrial Flutter: Tablet (SR): 324 mg every 8–12 hours, may increase dose with caution if necessary Atrial Fibrillation/Atrial Flutter-Cardioversion: Tablet (SR): Option 1: 1,648 mg every 8 hours; if no cardioversion after 3–4 doses, may increase dose with caution if necessary Option 2: 2,324 mg every 8 hours for 2 days, then 648 mg every 12 hours for 2 days, then 648 mg every 8 hours for up to 4 days IV: Infusion of 0.25 mg/kg/min until sinus rhythm restored Maximum dose: 10 mg/kg	Safety and efficacy in pediatrics have not been established.	Injection: 80 mg/ml Tablet (SR): 324 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Ventricular Arrhythmia: Tablet (SR): 324 mg every 8–12 hours, may increase dose with caution if necessary IV: Infusion of 0.25 mg/kg/min until sinus rhythm restored Maximum dose: 10 mg/kg		
Quinidine sulfate	Atrial Fibrillation/Atrial Flutter: Tablet: 200 mg every 6 hours; may increase dose with caution if necessary Tablet (SR): 300 mg every 8–12 hours Atrial Fibrillation/Atrial Flutter-Cardioversion: Tablet: 400 mg every 6 hours; if no cardioversion after 4–5 doses, may increase dose with caution Tablet (SR): 300 mg every 8–12 hours; may increase dose with caution if necessary Ventricular Arrhythmia: Tablet: 200 mg every 6 hours; may increase dose with caution if necessary Tablet (SR): 300 mg every 8–12 hours	Safety and efficacy in pediatrics have not been established.	Tablet: 200 mg 300 mg Tablet (SR): 300 mg

SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antiarrhythmic agents are summarized in Table 16.

Table 16. Comparative Clinical Trials with the Antiarrhythmic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cairns et al.[21] (1997) CAMIAT Amiodarone loading dose of 10 mg/kg in two divided doses daily for 2 weeks, followed by 300–400 mg daily for 3–5 months, then 200–300 mg daily for 4 months, and finally 200 mg daily for 5–7 days per week for 16 months vs placebo	DB, MC, PC, RCT Patients greater than 19 years who had an acute MI within the previous 6–45 days, and the development of new 40 ms Q-waves in ≥2 adjacent ECG leads or the development of a dominant R-wave in V1, 24 hour ambulatory ECG monitoring that recorded a mean of ≥10 VDPs per hour (≥18 hours of monitoring required), or at ≥1 run of VT	N=1,202 2 years	Primary: Resuscitated ventricular fibrillation (RVF) or arrhythmic death (AD) Secondary: AD, cardiac death and all-cause mortality	Primary: Twenty five patients receiving amiodarone compared to 39 patients receiving placebo experienced an RVF or AD (RR reduction, 38.2; 95% CI, –2.1 to 62.6; P=0.029). Secondary: Twenty four patients receiving amiodarone compared to 33 patients receiving placebo experienced an AD (RR reduction, 29.3; 95% CI, –19.6 to 58.2; P=0.097). Cardiac mortality was not statistically significant between amiodarone and the placebo groups (44 vs 55 patients respectively; RR reduction 22.0; 95% CI, –15.9 to 47.6; P=0.108). All cause mortality was not statistically significant between the amiodarone and placebo groups (57 vs 68 patients respectively; RR reduction, 18.3; 95% CI, –16.1 to 42.6; P=0.129).
Julian et al.[22] (1997) EMIAT Amiodarone 800 mg daily for 2 weeks, followed by 400 mg daily	DB, MC, PC, RCT Patients between the ages of 18–75 years who survived ≥5 days post documentation of an MI, LVEF of ≤40% on MUGA done 5–	N=1,486 2 years	Primary: All-cause mortality Secondary: Cardiac mortality, AD and AD plus resuscitated cardiac arrest	Primary: There was not a statistically significant difference in all-cause mortality between the amiodarone and placebo groups (102 vs 103 patients in group; risk ratio, 0.99; 95% CI, 0.76 to 1.31; P=0.96). Secondary: There was not a statistically significant difference in total cardiac mortality between the amiodarone and placebo groups (89 vs 85 patients; risk ratio, 0.94; 95% CI, 0.70 to 1.26; P=0.67).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 14 weeks, then 200 mg daily until the end of the study vs placebo	21 days after admission to the coronary-care unit			The amiodarone group had a lower number of patients who experienced an AD compared to the patients in the placebo group (50 vs 33 patients; risk ratio, 0.65; 95% CI, 0.42 to 1.00; P=0.05). The amiodarone group had a lower number of patients who experienced an AD and resuscitated cardiac arrest compared to the patients in the placebo group (61 vs 42 patients; risk ratio, 0.68; 95% CI, 0.46 to 1.00; P=0.05).
Deedwania et al.[23] (1998) CHF-STAT Amiodarone 800 mg QD for 2 weeks, then 400 mg QD for 50 weeks, then 300 mg QD vs placebo	DB, MC, PC Patients with history of heart failure (≥3 months), NYHA class II, III, or IV, LVEF ≤40%, evidence of dilated cardiomyopathy, dyspnea on exertion or history of paroxysmal nocturnal dyspnea, and frequent ventricular premature beats on 24-hour Holter monitoring	N=667 4.5 years	Primary: Rate control vs conversion to sinus rhythm in atrial fibrillation patients Secondary: Occurrence of new atrial fibrillation	Primary: From time points at 2 weeks and beyond, the ventricular rates of those patients in the amiodarone treatment group were significantly lower than those in the placebo group (P=0.001 at week 2, and P=0.006 at months 6 and 12). Of the patients that had atrial fibrillation at baseline, 16 patients in the amiodarone group compared to 4 patients in the placebo group, spontaneously converted to sinus rhythm (P=0.002). Secondary: Eleven patients in the amiodarone group compared 22 patients in the placebo group experienced new-onset atrial fibrillation (P=0.005). Patients in the amiodarone group who spontaneously converted to sinus rhythm and maintained it during the follow-up period had significantly lower mortality compared with those who remained in atrial fibrillation (P=0.04).
Kochiadakis et al.[25] (2004) Amiodarone 15 mg/kg QD for 7 days, followed by 10 mg/kg QD for 7 days, then tapered dose over 7–12 days to	RCT, SB Patients >18 years of age, ECG documentation of AF, symptoms such as light-headedness, palpitation, chest pain, and dyspnea in association with atrial fibrillation;	N=146 3 years	Primary: Time to adverse events (relapse to AF or intolerable side effects) whichever occurred first Secondary: Maintenance of atrial fibrillation	Primary: There was not a significant difference between the amiodarone and propafenone groups for the suppression of recurrent symptomatic atrial fibrillation or in side effects (P=0.44). Secondary: Amiodarone and propafenone were equally effective in maintaining sinus rhythm without side effects included (P=0.058).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
maintenance levels over 7-12 days to a maintenance dose of 200 mg QD vs propafenone 150-300 mg followed by a maintenance dose of 150 mg TID	successful chemical or electrical cardioversion to sinus rhythm in the patients with persistent atrial fibrillation		free time	
Gulizia et al.[32] (2008) PITAGORA Amiodarone 600 mg/day for 10 days, followed by 400 mg/day for 10 days, then 200 mg/day thereafter vs class Ic antiarrhythmic drugs (flecainide 200 mg/day, propafenone 450-600 mg/day)	RCT, SB, MC Patients with sinus node disease (SND), ≥3 episodes of symptomatic atrial tachyarrhythmias (AT) in the 12 months before enrollment, and ≥1 AT episode documented by electrocardiogram (ECG) or Holter recording	N=176 21 months	Primary: Composite of death, permanent AT, cardiovascular hospitalization, atrial cardioversion, or interruption of the randomly assigned antiarrhythmic drug (AAD) regimen Secondary: AT-related composite end point (consisting of permanent AT, hospitalizations due to AT recurrences, atrial cardioversions, and AAD discontinuation because of lack of	Primary: The primary end point occurred in 30.7% of patients in the class Ic group and 40.0% of patients in the amiodarone group (P=0.24). Secondary: Death occurred in 2.7% of patients receiving class Ic agents and 8.6% of patients receiving amiodarone (P=0.16). Twelve patients receiving amiodarone were hospitalized for cardiovascular causes compared to 9 patients receiving class Ic drugs. Ischemic stroke occurred in 2 amiodarone patients. After 1 year, the AT-related composite end point was 22% for amiodarone and 22% for class Ic agents (23% for propafenone and 21% for flecainide; P=0.1). After 1 year, freedom from AT episodes at >10 minutes, 1 day, and 7 days was 40%, 73%, and 91%, respectively, for amiodarone and 28%, 78%, and 86%, respectively for class Ic agents. The mean number of AT-related symptoms at the baseline was 2.0 in the amiodarone group and 2.2 in class Ic group. At the first follow-up visit, the mean number of AT-related symptoms decreased to 0.7 and 1.1, respectively (P<0.01). Quality of life scores improved from baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			efficacy), AT-related symptoms and QoL	values of 52 in the amiodarone group and 54 in the class Ic group to 67 and 67, respectively, at the first follow-up visit (P<0.01). There was no significant difference between the treatment groups with regards to AT-related symptoms and quality of life scores.
Torp-Pederson et al.[24] (1999) Dofetilide 250 mcg QD to 500 mcg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years hospitalized with new or worsening CHF and who had ≥1 episode of shortness of breath on minimal exertion or at rest or paroxysmal nocturnal dyspnea	N=1,518 1 year	Primary: Death from any cause Secondary: Death from cardiac causes, death from arrhythmia, death from cardiac causes or successful resuscitation after cardiac arrest, arrhythmias requiring treatment, worsening CHF and MI, and in patients with baseline atrial fibrillation, incidence of conversion to and maintenance of sinus rhythm	Primary: Death did not differ significantly between dofetilide treatment group and placebo (311 [41%] vs 317 [42%] respectively; HR, 0.95; 95% CI, 0.81 to 1.11; P=0.54). Secondary: There was not a significant difference in death from cardiac causes between dofetilide treatment group and placebo (33% vs 33%, respectively). There was not a significant difference in death from arrhythmias between dofetilide treatment group and placebo (20% vs 20%, respectively). Fewer hospitalizations due to worsening heart failure were experienced in the dofetilide group compared to placebo (30% vs 38% respectively). There was a statistically significant greater number of patients with atrial fibrillation at baseline who converted to sinus rhythm in the dofetilide compared to those patients with atrial fibrillation at baseline in the placebo group. At 1 month: 12% vs 2% respectively (P<0.001) and at 12 months: 44% vs 13% respectively (P<0.001). After cardioversion, more patients with baseline atrial fibrillation in the dofetilide group maintained sinus rhythm compared to those patients in the placebo group (HR, 0.35; 95% CI, 0.22 to 0.57; P<0.001).
Singh et al.[34] (2007) EURIDIS and ADONIS Dronedarone	RCT, MC, DB (European Trial – EURIDIS; Non-European Trial: ADONIS) Patients ≥21 years	N=1,237 1 year	Primary: Time from randomization to the first documented recurrence of atrial fibrillation	Primary: In the European trial, the median times from randomization to a documented recurrence of atrial fibrillation were 96 days in the dronedarone group and 41 days in the placebo group. At 12 months, 67.1% of patients in the dronedarone group and 77.5% of patients in the placebo group had had a recurrence of atrial fibrillation (HR, 0.78; 95% CI, 0.64 to 0.96; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
400 mg twice daily vs placebo	of age with at least one episode of atrial fibrillation in the preceding 3 months who were in sinus rhythm for at least 1 hour before randomization		Secondary: Symptoms related to atrial fibrillation during recordings of 12-lead electro-cardiography or transtelephonic monitoring and the mean ventricular rate during the first recurrence	In the non-European trial, the median times from randomization to a documented recurrence of atrial fibrillation were 158 days in the dronedarone group and 59 days in the placebo group. At 12 months, 61.1% of patients in the dronedarone group and 72.8% of patients in the placebo group had had a recurrence of atrial fibrillation (HR, 0.73; 95% CI, 0.59 to 0.89; P=0.002). In the combined European and non-European trials, the median times to a documented recurrence of atrial fibrillation were 116 days in the dronedarone group and 53 days in the placebo group. At 12 months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (HR, 0.75; 95% CI, 0.65 to 0.87; P<0.001). Secondary: In the European trial, 37.1% of patients in the dronedarone group and 47.5% of those in the placebo group had symptomatic recurrences of atrial fibrillation (P=0.006). In the non-European trial, symptomatic recurrences occurred in 38.3% of patients in the dronedarone group and 44.5% of those in the placebo group (P=0.02). In the combined European and non-European trials, the corresponding numbers were 37.7% and 46.0% (P<0.001). In the European trial, the mean ventricular rate during the first adjudicated recurrence was 102.3beats per minute in the dronedarone group and 117.5 beats per minute in the placebo group (P<0.001). In the non-European trial, the mean ventricular rate during the first adjudicated recurrence was 104.6 beats per minute in the dronedarone group and 116.6 beats per minute in the placebo group (P<0.001). In the European trial, 21.2% of patients in the dronedarone group were hospitalized or died at 12 months compared to 32.0% of those in the placebo group (HR, 0.66; 95% CI, 0.47 to 0.93; P=0.02). In the non-European trial, 24.5% of patients in the dronedarone group were hospitalized or died compared to 29.8% of those in the placebo group (HR, 0.80; 95% CI, 0.56 to 1.14; P=0.22). In the combined European and non-European trials, the corresponding numbers were 22.8% and 30.9%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(HR, 0.73; 95% CI, 0.57 to 0.93; P=0.01). There was a higher incidence of elevated serum creatinine levels in the dronedarone group than in the placebo group (2.4% vs 0.2%, P=0.004). Ventricular arrhythmias occurred infrequently in both groups and no episodes of torsades de pointes were reported.
Davy et al.[35] (2008) ERATO Dronedarone 400 mg twice daily vs placebo	RCT, DB, MC, PC Adult patients ≥21 years with documented, symptomatic permanent atrial fibrillation (AF), for which cardioversion was not considered an option	N=174 6 months	Primary: Change in mean ventricular rate measured by 24-hour Holter recording on day 14 Secondary: Change in mean ventricular rate during submaximal and maximal exercise at day 14, change in maximal exercise duration at day 14, change in mean ventricular rate measured by 24-hour Holter after 4 months, safety and tolerability	Primary: There was a mean reduction in mean 24-hour ventricular rate of 11.0 beat/min in the dronedarone group at day 14 compared to an increase of 0.7 beat/min in the placebo group (P<.0001). Secondary: There was a reduction in mean heart rate (HR) of 25.6 beat/min in the dronedarone group compared to 2.2 beat/min in the placebo group during submaximal exercise (P<0.0001). There was a reduction in mean HR of 27.4 beat/min in the dronedarone group compared to 2.9 beat/min in the placebo group at maximal exercise (P<0.0001). There was a mean increase in maximal exercise duration of 0.14 minutes and 0.26 minutes in the dronedarone and placebo groups, respectively (P=0.514). The mean change in 24-hour Holter-monitored ventricular HR was greater with dronedarone compared to placebo at 4 months (−10.1 beat/min vs −1.3 beat/min, respectively; P<0.001). Dronedarone was well tolerated throughout the study. There were no cases of torsades de pointes or sustained ventricular tachycardia reported in either treatment group. The incidence of treatment-emergent adverse events was higher with dronedarone than placebo. Gastrointestinal disturbances occurred in 20% of patients receiving dronedarone compared to 13.5% of those receiving placebo.
Køber et al.[38] (2008)	RCT, DB, PC, MC Patients ≥18 years	N=627 7 months	Primary: Death from any cause or	Primary: The data and safety monitoring board recommended that the trial be terminated early due to an excess of deaths in the dronedarone group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ANDROMEDA Dronedarone 400 mg twice daily vs placebo	of age who were hospitalized with new or worsening heart failure and who had had at least one episode of shortness of breath on minimal exertion or at rest (NYHA III or IV), paroxysmal nocturnal dyspnea, or a wall-motion index ≤1.2		hospitalization for worsening heart failure Secondary: Death from all causes, hospitalization for cardiovascular causes, hospitalization for worsening heart failure, occurrence of atrial fibrillation or flutter, death from arrhythmia, or sudden death	Death from any cause occurred in 8.1% of patients receiving dronedarone and 3.8% of patients receiving placebo (HR, 2.13; 95% CI, 1.07 to 4.25; P=0.03). The number of deaths that were attributed to arrhythmia or sudden death did not differ significantly between the two groups. The primary combined end point of all-cause mortality or hospitalization for worsening heart failure was not different between dronedarone and placebo (17.1% vs 12.6%, respectively; HR, 1.38; 95% CI, 0.92 to 2.09; P=0.12). Secondary: The total number of patients who had a first hospitalization for an acute cardiovascular cause was higher in the dronedarone group than in the placebo group (P=0.02). The main reason for hospitalization for a cardiovascular cause was worsening heart failure (49.3% in the dronedarone group and 60.0% in the placebo group). Other cardiovascular events requiring a first hospitalization in the dronedarone group compared to placebo were myocardial ischemia (18.3% vs 16.0%, respectively), ventricular arrhythmia (4.2% vs 4.0%, respectively), supraventricular arrhythmia (5.6% vs 2.0%, respectively), stroke (5.6% vs 6.0%, respectively), other cardiovascular events (12.7% vs 8.0%, respectively), and presumed cardiovascular events (4.2% vs 4.0%, respectively). There were no significant differences detected between the two groups with regards to serious adverse events, except for increases in the serum creatinine concentration, which were observed more frequently in the dronedarone group than in the placebo group. At the 1-month visit, 21.4% of the patients in the dronedarone group had atrial fibrillation compared to 24.8% of patients receiving placebo (P=NS). No cases of torsades de pointes were observed in either group.
Hohnloser et al.[36] (2009) ATHENA	RCT, DB, PC, MC Patients with paroxysmal or	N=4,628 21 months	Primary: First hospitalization due to cardiovascular	Primary: In the dronedarone group, 31.9% of patients experienced the primary outcome compared to 39.4% of patients in the placebo group (HR, 0.76; 95% CI, 0.69 to 0.84; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dronedarone 400 mg twice daily vs placebo	persistent atrial fibrillation or flutter with at least one of the following risk factors: ≥70 years of age, arterial hypertension (treated with at least 2 antihypertensive drugs), diabetes mellitus, previous stroke, transient ischemic attack, or systemic embolism, left atrial diameter ≥50 mm, and left ventricular ejection fraction≤40%		events or death Secondary: Death from any cause, death from cardiovascular causes, and hospitalization due to cardiovascular events	Secondary: Death from any cause occurred in 5.0% of patients in the dronedarone group and 6.0% of patients in the placebo group (HR, 0.84; 95% CI, 0.66 to 1.08; P=0.18). Cardiovascular death occurred in 2.7% of patients in the dronedarone group and 3.9% of patients in the placebo group (HR, 0.71; 95% CI, 0.51 to 0.98; P=0.03). In the dronedarone group, 29.3% of patients had a first hospitalization due to cardiovascular events compared to 36.9% of patients in the placebo group (HR, 0.74; 95% CI, 0.67 to 0.82; P<0.001). Bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and an increase in the serum creatinine level were significantly more common in the dronedarone group than in the placebo group. Pulmonary symptoms, interstitial lung disease, and abnormalities of thyroid function were not significantly more common with dronedarone than with placebo.
Piccini et al.[39] (2009) Dronedarone 400 mg twice daily vs amiodarone 200 mg once daily	MA Patients with atrial fibrillation	N=7,140 Mean 13-16 months	Primary: Recurrence of atrial fibrillation, all-cause mortality, and adverse events	Primary: <u>Dronedarone vs placebo</u> For prevention of atrial fibrillation, the effect of dronedarone had an OR of 0.79 (95% CI, 0.33 to 1.87), with a risk difference of -0.040 (95% CI, -0.19 to 0.11) equivalent to 40 fewer events per 1,000 patients treated. For mortality, the OR was 0.85 (95% CI, 0.66 to 1.11), with a risk difference of -0.003 (95% CI, -0.011 to 0.006). For adverse events requiring discontinuation, there was a significant increase over placebo with OR of 1.166 (95% CI, 1.36 to 2.02) and risk difference 0.045 (95% CI: 0.028 to 0.062). <u>Amiodarone vs placebo</u> Amiodarone significantly prevented atrial fibrillation, with an OR of 0.12 (95% CI, 0.08 to 0.19) and a risk difference of -0.401 (95% CI: -0.46 to -0.34) equivalent to 401 fewer events per 1,000 patients treated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For mortality, the OR was 1.88 (95% CI, 0.54 to 6.56), with a risk difference of 0.005 (95% CI: -0.016 to 0.026). For adverse events requiring discontinuation, there was a significant increase over placebo with an OR of 11.04 (95% CI: 1.89 to 64.5) and risk difference of 0.128 (95% CI, 0.023 to 0.230). <u>Dronedarone vs amiodarone</u> In the indirect meta-analysis, amiodarone significantly reduced the risk of recurrent atrial fibrillation compared with dronedarone (OR, 0.16; 95% CI, 0.06 to 0.42), with a risk difference of -0.36 (95% CI, -0.52 to -0.19), which is equivalent to 360 fewer events per 1,000 patients treated. This was consistent with the direct results from DIONYSOS (OR, 0.44; 95% CI, 0.30 to 0.64), with a risk difference of -0.186 (95% CI: -0.266 to -0.1028). There was a mortality trend favoring dronedarone in the indirect meta-analysis (amiodarone vs. dronedarone OR, 2.20; 95% CI, 0.61 to 7.88; risk difference: 0.008; 95% CI: -0.015 to 0.030). This finding was consistent with the DIONYSOS trial (OR, 2.44; 95% CI, 0.48 to 12.6), risk difference 0.011 (95% CI, -0.010 to 0.033). For adverse effects requiring interruption of therapy, the indirect meta-analysis estimate favored dronedarone; amiodarone was associated with an increased odds of study drug termination (OR, 6.65; 95% CI, 1.13 to 39.3) with a risk difference of 0.083 (95% CI, -0.022 to 0.1866). The effect was similar in DIONYSOS (OR, 2.24; 95% CI, 1.13 to 4.43) with a risk difference of 0.057 (95% CI, 0.010 to 0.105). The incidence of thyroid toxicity (4% vs. 3%), symptomatic bradyarrhythmias (2.8% vs. 1.1%), and hepatotoxicity (3.5% vs. 2.5%) leading to treatment discontinuation were comparable between dronedarone and placebo. There were no cases of torsades de pointes in any of the patients administered amiodarone or in the DIONYSOS trial. There was a single case of torsades de pointes in a patient receiving dronedarone in ATHENA.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cast Investigators[26-27] (1993 and 1989) CAST I Encainide 35–50 mg TID, flecainide 100–150 mg BID or moricizine 200–250 mg TID vs placebo	MC, OL, PC, RCT Patients 6 days to 2 years post documented MI who had ≥6 VDPs per hour during an ambulatory ECG recording, and a LVEF of ≤55% if recorded 6–90 days after MI, or ≤40% if recorded 90 days-2 years post-MI	N=2,371 1 year	Primary: Overall survival and free of cardiac arrest or AD	Primary: After 1 year of therapy 90% of patients in the active treatment group survived compared to 95% of patients in the placebo group (P=0.0006). A higher total mortality rate was seen in the encainide and flecainide groups: 56 patients (7.7%) taking encainide or flecainide compared to 22 patients (3.0%) taking placebo (RR, 2.5; 95% CI, 1.6 to 4.5). After 1 year of therapy, 93% of patients in the active treatment group were free of cardiac arrest or AD compared to 96% of patients in the placebo group (P=0.003). Encainide and flecainide accounted for the excess of deaths from arrhythmia and nonfatal cardiac arrests: 33 patients (4.5%) taking encainide or flecainide compared to 9 patients (1.2%) taking placebo (RR, 3.6; 95% CI, 1.7 to 8.5). After a mean follow up of 10 months, due to a significantly higher death rate in the active treatment group (63 patients) compared to the placebo group (26 patients; P=0.000), the flecainide and encainide arms of this trial were stopped early. Also, death or cardiac arrest due to arrhythmia was significantly higher in the active treatment group (43 patients) compared to the placebo group (16 patients; P=0.0004).
Kosior et al.[37] (2009) Propafenone 600 mg orally, followed by 300 mg after eight hours if sinus rhythm had not been restored by then vs	RCT, SC Patients 18-85 years of age admitted to the Emergency Department with symptomatic recent onset atrial fibrillation (AF) <48 hours duration, mean ventricular rate >70 beats per minute, and NYHA functional class <II	N=81 24 hours	Primary: Restoration of sinus rhythm (SR) and safety	Primary: Within the first 24 hours, SR was restored in 90.7% of patients receiving propafenone and in 91.4% of patients receiving digoxin/quinidine. There was no significant difference in the efficacy after 24 hours of follow-up (90.1% vs 91.4%, respectively; P=0.78). Propafenone was more effective at restoring SR than digoxin/quinidine during the first eight hours (83.3% vs 54.3%, respectively; P<0.01). No life-threatening adverse events were reported during the follow-up. There was no difference in mild adverse events with propafenone compared to digoxin/quinidine (37.2% vs 45.7%, respectively; P=0.56). No case of significant heart failure exacerbation was observed.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
digoxin 1 mg IV, followed by an oral loading of quinidine (400 mg, then 200 mg every 2 hours)				
Wyse et al.[28] (2002) AFFIRM Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm) vs rate control therapy: β-blockers, calcium-channel blockers, digoxin, and combinations of these drugs	MC, RCT Patients 65 years and older who had atrial fibrillation that was likely recurrent, atrial fibrillation was likely to cause illness or death, long-term treatment for atrial fibrillation was warranted, no contraindicated to anticoagulation therapy, eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomization	N=4,060 3.5 years	Primary: Overall mortality Secondary: Composite death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest	Primary: The difference in mortality between the two groups was not statistically significant (HR, 1.15; 95% CI, 0.99 to 1.34; P=0.08). Secondary: The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups (P=0.33).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(doses not specified and adjusted to maintain normal sinus rhythm)				
Van Gelder et al.[29] (2002) RACE Rhythm control therapy: electrical cardioversion, then sotalol 160-320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200-300 mg QD or propafenone 450-900 mg QD; if recurrence again, electrical cardioversion repeated along with amiodarone 600 mg QD for 4 weeks then 200 mg QD vs rate control	MC, RCT Patients with recurrent persistent atrial fibrillation or atrial flutter, who have undergone one electrical cardioversion during the previous two years, with a maximum of two	N=522 2 years	Primary: Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic drugs	Primary: The composite end point occurred in 44 (17.2%) patients in rate-control group and in 60 (22.6%) patients in the rhythm-control group (absolute difference of –5.4; 90% CI, –11.0 to 0.4). Death from cardiovascular causes occurred in 18 (7.0%) patients in rate-control group and in 18 (6.8%) patients in the rhythm-control group (absolute difference of 0.2; 90% CI, –3.4 to 3.9). HF occurred in 9 (3.5%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of –1.0; 90% CI, –3.8 to 1.8). Thromboembolic complications occurred in 14 (5.5%) patients in rate-control group and in 21 (7.9%) patients in the rhythm-control group (absolute difference of –2.4; 90% CI, –6.0 to 1.2). Bleeding occurred in 12 (4.7%) patients in rate-control group and in 9 (3.4%) patients in the rhythm-control group (absolute difference of 1.3; 90% CI, –1.5 to 4.1). Severe adverse effects of antiarrhythmic drugs occurred in 2 (0.8%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of –3.7; 90% CI, –6.0 to –1.4). A pacemaker was implanted in 3 (1.2%) patients in rate-control group and in 8 (3.0%) patients in the rhythm-control group (–1.8; 90% CI, –3.9 to 0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy: digitalis, non-dihydropyridine calcium channel blocker, and β-blocker, alone or in combination				
Opolski et al.[30] (2004) HOT CAFÉ Rhythm control therapy: propafenone 450–600 mg QD, disopyramide 300–600 mg QD or sotalol 160–320 mg QD vs rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin, or a combination of these drugs. All patients underwent electric cardioversion prior to the initiation of study medication.	MC, OL, RCT Patients between 50–75 years of age with atrial fibrillation known to be present continuously for between 7 days and 2 years with acceptable etiology of the arrhythmia related to ischemic heart disease, arterial hypertension, hemodynamically insignificant valvular heart disease, or lack of assessable etiology	N=205 1 year	Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage) Secondary: Rate control, sinus rhythm maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage, hospitalization, new or worsening CHF, or changes in exercise tolerance	Primary: There was not a significant difference in composite of death from any cause between the rate control group and the rhythm control group (OR, 1.98; 95% CI, 0.28 to 22.3; P>0.71). Secondary: The patients in the rhythm control group had a significantly lower mean heart rate (79.1 ± 8.6 beats/min) in 24 hour Holter monitoring compared to the patients in the rate control group (85.8 ± 7.5 beats/min; P<0.003). Four patients in the rhythm control group experienced proarrhythmic effects. Whether this lead to discontinuation of therapy was not mentioned. At the end of the study, 66 patients (63.5%) in the rhythm control arm were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion. There was not a statistical difference seen in bleeding complications between the rhythm control group (8 patients) and rate control group (5 patients). A significantly lower number of hospitalizations were seen in the rate control arm compared to the rhythm control arm (12% vs 74%, respectively; P<0.001). Both the rhythm control group and rate control group had significant improvements in CHF class at some point during follow-up compared to baseline (P<0.001 and P<0.05, respectively). No difference in NYHA

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				functional class between patients initially randomized to the two strategies was found at the end of the follow-up period. At the end of the study, both maximal workload and exercise duration were higher in the rhythm control arm compared to the rate control arm (P<0.001 and P<0.001, respectively).
Shelton et al.[31] (2009) CAFE´-II Rhythm control therapy: amiodarone therapy (200 mg three times daily for 1 month, then 200 mg twice daily for 1 month and 200 mg daily thereafter) vs rate control therapy: digoxin and β-blockers Cardioversion was allowed if patients in the rhythm control group remained in atrial fibrillation despite amiodarone therapy.	RCT, MC Patients aged >18 years of age with persistent atrial fibrillation and chronic symptomatic heart failure (NYHA >Class II symptoms) with evidence of systolic dysfunction on echocardiography	N=61 1 year	Primary: Quality of life (QoL) using the Medical Outcomes Study Short Form-36 version II (SF-36vII) questionnaire Secondary: Proportion of patients in sinus rhythm (SR), scores on the Minnesota Living with Heart failure (MLWHF) questionnaire, NTproBNP, 6-minute corridor walk test (6MWT) and severity of LV systolic dysfunction	Primary: Patients assigned to rhythm control had a greater improvement in QoL over 1 year compared with rate control (P=0.020 for SF36vII as a whole; P=0.050 for mental functioning and P=0.029 for physical functioning subgroups). Secondary: At 1 year, target ventricular rate control was achieved in 90% of patients assigned to the rate control group. Digoxin and β-blocker use at 1 year was 84% and 90%, respectively. All patients in the rate control group were in atrial fibrillation at each and every follow-up visit. Sinus rhythm was restored in 20% of patients using amiodarone alone. Cardioversion restored SR in 78% patients in whom it was attempted. Overall, 87% of patients were converted from atrial fibrillation to SR at some time during the study. he prevalence of atrial fibrillation in the rhythm control group was 53% at 4 months, 30% at 8 months and 34% at 1 year. The difference in QoL using the MLWHF questionnaire was not significant in patients assigned to rhythm control vs rate control (P=0.140). The median NTproBNP concentrations at 1 year were 1480 pg/ml and 685 pg/ml for rate and rhythm groups, respectively. A greater reduction was seen for those in the rhythm control group compared with rate control (P=0.047). The mean change in distance walked at 1 year was 27 meters and +5 meters for rate and rhythm control, respectively (P=0.342).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients assigned to rhythm control had a greater improvement in LV function over 1 year compared with patients assigned to rate control (P=0.014).
Lafuente-Lafuente et al.[33] (2009) Antiarrhythmic drugs (amiodarone, aprindine, azimilide, bidisomide, flecainide, disopyramide, dofetilide, dronedarone, quinidine, propafenone, sotalol) vs placebo, drugs for rate control (digoxin, calcium channel blockers, β-blockers) or no treatment	MA Adults >16 years of age who had atrial fibrillation of any type and duration and in whom sinus rhythm had been restored, spontaneously or by any therapeutic intervention	N=12,559 (45 trials) Variable duration	Primary: Mortality, embolic complications, adverse events Secondary: Use of anticoagulation, recurrence of atrial fibrillation	Primary: No deaths were reported with flecainide in the three trials. Quinidine showed a trend to increase mortality compared to controls (OR, 2.26; 95% CI, 0.93 to 5.45; P=0.07). This trend was significant if missing patients were counted as deaths (OR, 2.29; 95% CI, 1.05 to 5.01; P=0.04), and when class IA drugs (quinidine and disopyramide) were combined (OR, 2.39; 95% CI 1.03 to 5.59; P=0.04). The number needed to harm (NNH) for class IA drugs was 109 patients treated for 1 year to have 1 excess death. Sotalol showed a trend to increased mortality (OR, 2.09; 95% CI, 0.97 to 4.49; P=0.06) compared with controls. This trend was significant if missing patients were counted as deaths (OR, 2.27; 95% CI, 1.36 to 3.77; P=0.002). Amiodarone was associated with a reduction in mortality compared with combined class I drugs (OR, 0.39; 95% CI, 0.19 to 0.79; NNT 17). When compared with controls, amiodarone showed no significant difference in mortality. No other significant difference in mortality was detected, either versus control or between different antiarrhythmics. The analysis of cardiovascular mortality gave the same results as that of all-cause mortality. Only five of the 30 studies comparing antiarrhythmics with a control reported stroke outcomes. They reported six strokes in 650 patients in the control groups and 20 strokes in 1755 patients treated with antiarrhythmics. Withdrawals due to adverse effects were more frequent with all drugs, except aprindine and dofetilide, compared to controls. Pooled events rates varied from 9% to 23% for withdrawals due to adverse effects. The mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				number of patients needed to treat for 1 year to have 1 excess withdrawal from treatment ranged from 9 (quinidine) to 27 (amiodarone, propafenone, or sotalol). Quinidine caused more withdrawals than the other class I drugs (OR, 2.25; 95% CI 1.45 to 3.51; P=0.0003). Amiodarone produced significantly fewer withdrawals than other class I drugs combined (OR, 0.52; 95% CI, 0.34 to 0.81; P=0.004). All antiarrhythmics increased proarrhythmic effects, with the exception of amiodarone and propafenone. Pooled events rates varied from 1% to 7% for proarrhythmia. The NNH for proarrhythmia ranged between 17 (flecainide) and 119 (dofetilide). Amiodarone produced significantly less proarrhythmic events than other class I drugs combined (OR, 0.28; 95% CI, 0.13 to 0.59; P=0.0007). Secondary: All class IA, class IC and class III drugs significantly reduced the recurrence of atrial fibrillation. Pooled recurrence rates of atrial fibrillation at 1 year were 71% to 84% in controls and were reduced to 42% to 67% in patients treated with antiarrhythmics. The NNT for 1 year to avoid 1 recurrence of atrial fibrillation were 3 with amiodarone, 4 with flecainide, 5 with dofetilide and propafenone, 8 with quinidine and sotalol and 10 with dronedarone. Amiodarone reduced recurrences of atrial fibrillation significantly more than combined class I drugs (OR, 0.31; 95% CI, 0.21 to 0.45; P<0.0001) and more than sotalol (OR, 0.43; 95% CI 0.29 to 0.64; P<0.0001). No other differences between antiarrhythmics were detected. Chronic anticoagulation with warfarin was mandatory in only three studies. The decision on anticoagulation was left to the judgment of the attending physician in the remaining studies.

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized control trial, SB=single-blinded
Miscellaneous abbreviations: AD=arrhythmic death, AF=atrial fibrillation, CAST=Cardiac Arrhythmia Suppression Trial, CHF=congestive heart failure, ECG=electrocardiographic, HF=heart failure, HR=hazard ratio, LVEF=left ventricular ejection fraction, MI=myocardial infarction, MUGA=multiple-gated nuclear angiography, NYHA=New York Heart Association, OR=odd ratio, RR=relative risk, RVF=resuscitated ventricular fibrillation, VDPs=ventricular premature depolarizations, VT=ventricular tachycardia

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 17. Relative Cost of the Antiarrhythmic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amiodarone	injection, tablet	Cordarone®*, Pacerone®*	$$-$$$$$	$-$$$
Disopyramide	capsule, sustained-release capsule	Norpace®*, Norpace CR®*	$$$$	$$-$$$$
Dofetilide	capsule	Tikosyn®	$$$$	N/A
Dronedarone	tablet	Multaq®	$$$$$	N/A
Flecainide	tablet	Tambocor®*	$$$$-$$$$$	$$-$$$
Mexiletine	capsule	N/A	N/A	$-$$
Propafenone	sustained-release capsule, tablet	Rythmol®*, Rythmol SR®	$$$$	$$$
Quinidine	injection, sustained-release tablet, tablet	N/A	N/A	$-$$$

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

X. Conclusions

The antiarrhythmic agents are effective for the treatment of atrial fibrillation/flutter and ventricular arrhythmias. These agents differ with regards to their FDA-approved indications, mechanism of action, pharmacokinetic properties, drug interactions and adverse events. All of the antiarrhythmic agents are available in a generic formulation, with the exception of dofetilide and dronedarone.

There are several organizations that provide recommendations on the use of the antiarrhythmic agents. Treatment options for atrial fibrillation include anticoagulation, ventricular rate control and drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies.[15, 28-30] Rate control may be preferred for older patients with persistent atrial fibrillation who have hypertension or heart disease.[15] Rhythm control may be preferred in younger patients with lone atrial fibrillation or in those whose quality of life has been affected.[15] Ideally, antiarrhythmic agents should reduce symptoms, prevent recurrent atrial fibrillation and have a low incidence of toxicity.[19] However, all of the antiarrhythmic agents can cause serious complications. Initial and long-term management strategies differ from one patient to another. The specific antiarrhythmic agent that is recommended for the treatment of atrial fibrillation depends upon the patient's comorbidities and cardiac history, as well as adverse effects (refer to Table 2 for further discussion). The antiarrhythmic agents are generally not recommended for the initial treatment of ventricular arrhythmias; however, they may be effective as adjunctive therapy in certain situations.[16] These agents have not been shown to improve mortality in patients with atrial or ventricular arrhythmias.[7-13]

Amiodarone is an effective treatment option for atrial fibrillation; however, its use is limited by toxicity (pulmonary, thyroid and gastrointestinal), photosensitivity reactions and bluish discoloration of the skin. Amiodarone is associated with a low risk of proarrhythmia in patients with left ventricular hypertrophy, heart failure, coronary artery disease and previous myocardial infarction. Studies also support the efficacy of dofetilide for the prevention of atrial fibrillation/flutter. To reduce the risk of early proarrhythmia, dofetilide must be initiated in the hospital.[10] Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.

Dronedarone is a new antiarrhythmic agent, which was approved by the FDA in July 2009. It is a non-iodinated analog of amiodarone, and as a result, it is less lipophilic and has a shorter half-life than amiodarone. These structural changes were made to reduce the risk of thyroid and pulmonary toxicity. Clinical trials have shown that dronedarone reduces the risk of recurrent atrial fibrillation/flutter and is effective for the long-term maintenance of sinus rhythm.[34-36] However, the ANDROMEDA trial was terminated early due to an excess number of deaths in patients with heart failure who received dronedarone.[38] Death from any cause occurred in 8.1% of patients receiving dronedarone and 3.8% of patients receiving placebo (HR, 2.13; 95% CI, 1.07 to 4.25; P=0.03). As a result, dronedarone is contraindicated in patients with New York Heart Association (NYHA) class IV heart failure or NYHA class II to III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.[11] In a comparative study, dronedarone was found to be less effective than amiodarone for the composite end point of atrial fibrillation recurrence or premature drug discontinuation for intolerance or lack of efficacy.[39-40] There were fewer thyroid and neurological adverse events with dronedarone, as well as fewer patients discontinuing therapy due to adverse events compared to amiodarone. There were no studies found in the medical literature which evaluated the use of dronedarone for the prevention or treatment of ventricular arrhythmias.

There is insufficient evidence to support that one brand antiarrhythmic agent is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antiarrhythmic agents 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 antiarrhythmic agent 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 Cardiotonic Agents
AHFS Class 240408
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I. Overview

Digoxin is the only cardiotonic agent that is currently available. It inhibits sodium-potassium ATPase, which increases the intracellular concentration of sodium and calcium.[4-6] This leads to an increase in the force/velocity of myocardial contractions, decreased activation of the sympathetic nervous system and renin-angiotensin system, as well as a decrease in heart rate and conduction velocity through the atrioventricular (AV) node.[4-6] Digoxin is an effective treatment for heart failure due to its positive inotropic and neurohormonal deactivating effects. It is also beneficial for atrial arrhythmias due to its vagomimetic actions.[4-6] In high doses, digoxin increases sympathetic outflow from the central nervous system, which may lead to toxicity.[4-6]

The cardiotonic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Digoxin injection, solution and tablets are all available in a generic formulation. This class was last reviewed in May 2008.

Table 1. Cardiotonic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Digoxin	injection, solution, tablet	Lanoxin®*, Lanoxin Pediatric®	digoxin

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cardiotonic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cardiotonic Agents

Clinical Guideline	Recommendation(s)
Institute for Clinical Symptoms Improvement (ICSI): **Atrial Fibrillation**[9] **(2008)**	General Considerations • The goals of therapy in the management of atrial fibrillation include relief of symptoms, prevention of stroke, and prevention of tachycardia-mediated cardiomyopathy. Acute Rate Control • β-blockers are preferred for pharmacologic rate control, especially in patients with atrial fibrillation and heart failure. • Calcium channel blockers are alternative rate control agents when β-blockers are contraindicated. • Digoxin is a third-line agent for rate control. Digoxin does not lower blood pressure and has a positive inotropic effect. However, it works more slowly than β-blockers and calcium channel blockers, has no effect on the sympathetically mediated enhancement of atrioventricular node conduction during exercise, and is no better than placebo for conversion to normal sinus rhythm. Antiarrhythmic/Chemical Cardioversion • Pharmacologic therapy aimed at restoring sinus rhythm is often helpful in patients with atrial fibrillation. • Agents with proven efficacy for pharmacological cardioversion of atrial fibrillation of up to seven days duration include dofetilide, flecainide, ibutilide, propafenone and amiodarone. Digoxin should not be administered.

Clinical Guideline	Recommendation(s)
	• Agents with proven efficacy for pharmacological cardioversion of atrial fibrillation for more than seven days include dofetilide, amiodarone and ibutilide. Digoxin should not be administered. Treatment of Chronic Atrial Fibrillation • Drugs that can be used for rate control of chronic atrial fibrillation include β-blockers, non-dihydropyridine calcium channel blockers and digitalis. • Strategies aimed at maintaining sinus rhythm offered no significant advantages over rate control strategies, but were associated with a higher incidence of hospitalization and adverse drug effects. These trials indicate that a rate control strategy is acceptable, particularly in older patients who are asymptomatic or minimally symptomatic. • β-blockers are preferred for pharmacologic rate control. β-blockers control heart rate at rest and with exercise and also provide cardioprotective benefits. • Calcium channel blockers are alternative rate control agents when β-blockers are contraindicated. Calcium channel blockers control heart rate at rest and with exercise but may exacerbate systolic heart failure. • Digoxin is a third-line agent for rate control and can be used for patients with systolic congestive heart failure. • Digoxin does not lower blood pressure and has a positive inotropic effect; however, it works more slowly than β-blockers and calcium channel blockers, has no effect on the sympathetically mediated enhancement of atrioventricular node conduction during exercise, and is no better than placebo for conversion to normal sinus rhythm.
American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC): **Guidelines for Management of Patients with Atrial Fibrillation[10] (2006)**	• Oral digoxin may effectively control the heart rate at rest in patients with atrial fibrillation and is indicated for patients with heart failure, left ventricular dysfunction, or for sedentary individuals. • Digoxin is no longer considered first-line therapy for rapid management of atrial fibrillation, except in patients with heart failure or left ventricular dysfunction. It may also be an option for patients who are sedentary. • To control heart rate, digoxin use concurrently with either a β-blocker or nondihydropyridine CCB is reasonable in patients with atrial fibrillation, both at rest and during exercise. The medication chosen should be individualized and bradycardia should be avoided by closely monitoring and changing digoxin therapy. • Concurrent use of digoxin and β-blockers appears to be more effective than the concurrent use of digoxin and a CCB. • It is not recommended to use digoxin for pharmacological cardioversion of atrial fibrillation as harm may be caused. • Digitalis glycosides have not been proven to be more efficacious than placebo for the conversion of recent-onset atrial fibrillation to sinus rhythm. Digoxin may actually prolong the duration of paroxysmal atrial fibrillation episodes in some patients. • Evidence does not support the use of digitalis to suppress recurrent atrial fibrillation in most patients.
National Institute for Health and Clinical Excellence (NICE): **Atrial Fibrillation[11] (2006)**	• For patients who need rate control for chronic atrial fibrillation, β-blockers and calcium channel blockers are first line agents. Digoxin should only be used as first-line in sedentary patients or in those who cannot tolerate β-blockers or CCBs. • For patients who are prescribed digoxin alone for rate control, a diagnosis should be written on the prescription. • Combination therapies such as digoxin/β-blocker or digoxin/CCB may be considered once a patient has failed monotherapy.

Clinical Guideline	Recommendation(s)
	• Digoxin has been proven to be infective in pharmacological cardioversion and therefore is determined to be an inappropriate therapy for this indication. • Digoxin should not be used in atrial fibrillation patients who are hemodynamically unstable due to its slow onset of action. • The use of digoxin in patients with Wolff-Parkinson-White (WPW) syndrome is contraindicated due to the potential of exacerbating a rapid atrial fibrillation. • Digoxin has not been clinically proven to be effective in preventing postoperative atrial fibrillation therefore should not be used in this indication.
American College of Chest Physicians (ACCP): **Guidelines for Prevention and Management of Postoperative Atrial Fibrillation after Cardiac Surgery**[12] **(2005)**	• β-Blockers and nondihydropyridine CCBs are recommended as first- and second line agents to control ventricular response rate in atrial fibrillation after cardiac surgery. Digoxin has shown little efficacy in this patient population. • Current medical evidence does not support the use of digitalis for the prevention of postoperative atrial fibrillation. • No recommendation can be made regarding the use of digoxin for rhythm control of postoperative atrial fibrillation or atrial flutter.
American Academy of Family Physicians (AAFP)/American College of Physicians (ACP): **Management of Newly Detected Atrial Fibrillation**[7] **(2003)**	• For patients with atrial fibrillation, the following drugs are recommended for their demonstrated efficacy in rate control during exercise and while at rest: atenolol, metoprolol, diltiazem, and verapamil. Digoxin is only effective for rate control at rest and therefore should only be used as a second-line agent for rate control in atrial fibrillation. • Combinations of digoxin plus diltiazem, atenolol, or betaxolol have also been shown to be effective at rest and with exercise, but these may be better reserved for occasions when single agent therapy has failed.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: Guidelines for the Diagnosis and Management of Chronic Heart Failure in Adults**[8] **(2009)**	• It is reasonable to treat patients with atrial fibrillation and heart failure with a strategy to maintain sinus rhythm or with a strategy to control ventricular rate alone. • Digoxin may be beneficial in patients with current or prior symptoms of heart failure and reduced LVEF to decrease hospitalizations for heart failure. • Digoxin slows atrioventricular conduction more effectively at rest than during exercise, but does not block exercise-induced tachycardia that may limit the functional capacity of patients with heart failure. • β-blockers are more effective than digoxin during exercise and are preferred because of their favorable effects on the natural history of heart failure. • The combination of digoxin and β-blockers may be more effective than β-blockers alone for rate control. • Refer to the 2005 guidelines for additional information regarding the use of digoxin in patients with heart failure.[33]
Institute for Clinical Systems Improvement (ICSI): **Heart Failure in Adults**[15] **(2009)**	<u>Treatment of Systolic Dysfunction</u> • The cornerstone of treatment is the use of β-blockers and ACE inhibitors. • Patients who are intolerant of ACE inhibitors may benefit from the combination of hydralazine and nitrates. This treatment has been shown to improve survival compared to placebo, but is less effective than ACE inhibitors. ARB's are recommended for patients intolerant of ACE inhibitors. • The combination of hydralazine and nitrates is recommended in African Americans with moderate-to-severe symptoms on optimal therapy with ACE inhibitors, β-blockers and diuretics.

Clinical Guideline	Recommendation(s)
	• Digoxin improves symptoms for patients in sinus rhythm with ventricular dilatation, elevated filling pressures and a third heart sound. • Digoxin improves symptoms, exercise tolerance and quality of life but does not increase or decrease mortality. • Digoxin is beneficial in heart failure patients with reduced LVEF to decrease hospitalizations for heart failure. • Diuretics should be used to control fluid retention. • Aldosterone antagonists have been shown to reduce mortality. The addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of heart failure and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. <u>Treatment of Heart Failure with Preserved Ejection Fraction (HFPEF)</u> • Drugs used to treat systolic dysfunction (ACE, ARBs, diuretics, β-blockers) are generally used in patients with heart failure with preserved systolic function to treat comorbidities. <u>Atrial Fibrillation in Heart Failure</u> • β-blockers and digoxin used alone or in combination are the drugs of choice for achieving rate control. • Digoxin is effective in controlling ventricular rate at rest, but may not achieve satisfactory rate control with exertion. <u>Acute Treatment of Heart Failure</u> • Digoxin, as an inotrope, is not useful in the acute management of decompensated heart failure.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[14] **(2008)**	• In patients in sinus rhythm with symptomatic heart failure and LVEF ≤40%, treatment with digoxin (in addition to an ACE inhibitor) improves ventricular function, reduces hospital admission for worsening heart failure, but has no effect on survival. • Digoxin is useful for initial control of the ventricular rate in a patient with rapid atrial fibrillation and may be considered in patients with decompensated heart failure prior to initiation of a β-blocker. • The use of a β-blocker, alone or in combination with digoxin, is the preferred long-term treatment for rate control in patients with atrial fibrillation and LVEF ≤40%. • Digoxin controls the ventricular rate at rest, but does not provide sufficient rate control during exercise. • In patients with an LVEF >40%, verapamil or diltiazem may be used alone or in combination with digoxin to control the ventricular rate.
Heart Failure Society of America (HFSA): **Comprehensive Heart Failure Guideline**[13] **(2006)**	• Digoxin should be considered for patients with LV systolic dysfunction (left ventricular ejection fraction [LVEF] <40%) who have signs or symptoms of heart failure while receiving standard therapy, including ACE inhibitors and β-blockers: New York Heart Association (NYHA) class II-III and IV. • It is recommended that the dose of digoxin, which should be based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL • Doses greater than 0.25 mg daily for rate control are not recommended. • It is recommended that patients taking amiodarone and digoxin concurrently, that the maintenance dose of digoxin be reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended.

Clinical Guideline	Recommendation(s)
American College of Cardiology (ACC)/American Heart Association (AHA): **2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult**[33] **(2005)**	• Digoxin should not be used in patients with low EF, sinus rhythm, and no history of heart failure symptoms, because in this population, the risk of harm is not balanced by any known benefit. • There are no data to recommend the use of digoxin in patients with asymptomatic reduction of LVEF, except in those with atrial fibrillation. • Most patients with heart failure should be routinely managed with a combination of a diuretic, an ACE inhibitor or an ARB, and a β-blocker. Therapy with digoxin as a fourth agent may be initiated at any time to reduce symptoms, prevent hospitalization, control rhythm, and enhance exercise tolerance. • Digoxin therapy may be delayed until the patient remains symptomatic despite therapy with the neurohormonal antagonists or delay digoxin therapy until the symptomatic patient has tried and did not respond or could not tolerate aldosterone antagonist as well. • Digoxin should be considered an adjunct therapy to β-blockers for rate control in patients with chronic atrial fibrillation because β-blockers improve survival and may be effective at controlling rate alone. • In patients with an acute exacerbation of heart failure symptoms, patient should be initially treated with appropriate heart failure therapy, and once stable, digoxin may be initiated as part of a long-term treatment plan. • Digoxin should be avoided in patients with significant sinus or atrioventricular (AV) block (unless patient has pacemaker) and it should be used cautiously in patients who are on other agents that may suppress sinus or AV nodal function or affect digoxin levels.
National Institute for Health and Clinical Excellence (NICE): **Management of Chronic Heart Failure in Adults in Primary and Secondary Care**[16] **(2003)**	• First line therapy for patients with heart failure is an ACE inhibitor or ARB (if ACE inhibitor is not tolerated). • Digoxin may be added to concurrent therapy with a diuretic, ACE inhibitor, ARB, or β-blocker if the patient remains symptomatic and is in sinus rhythm. • If a patient has symptomatic heart failure and atrial fibrillation, digoxin should be used as the first line agent. • Digoxin is recommended for patients with worsening or severe heart failure due to LV systolic dysfunction despite therapy with ACE inhibitor, β-blocker and diuretic therapy. • Digoxin is recommended in patients with atrial fibrillation and any degree of heart failure. • Serum potassium should be monitored when patients are on digoxin therapy. • It is not recommended to obtain serum digoxin levels on a routine basis. A digoxin level drawn between 8–12 hours after the last dose may supply useful information to determine toxicity or non-compliance. • Reminder that patient's may experience signs of toxicity even if there digoxin level is in the recommended therapeutic range.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cardiotonic agents 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 Cardiotonic Agents[1-6]

Indication	Digoxin
Treatment of mild to moderate heart failure	✔
Control of ventricular response rate in patients with chronic atrial fibrillation	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the cardiotonic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cardiotonic Agents[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (days)
Digoxin	Oral: 60-80	20-25	Liver (16)	Renal (57-80) Bile (6-8) Feces (3-5)	1.3-2.2

V. Drug Interactions

Significant drug interactions with the cardiotonic agents are listed in Table 5.

Table 5. Significant Drug Interactions with the Cardiotonic Agents[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Digoxin	1	Amiodarone	Serum digoxin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of digoxin. Mechanism of interaction is unknown.
Digoxin	1	Amphotericin B	Amphotericin B-induced hypokalemia may increase the risk of digoxin toxicity.
Digoxin	1	Protease inhibitors	Protease inhibitors may increase plasma concentrations and pharmacologic effects of digoxin. Although the exact mechanism is unknown, P-glycoprotein inhibition by protease inhibitors may enhance the absorption and decrease the renal excretion of digoxin.
Digoxin	1	Macrolides and ketolides	Macrolides and ketolides may increase serum concentrations and toxic effects of digoxin. Inhibition of the P-glycoprotein transport system by macrolides and ketolides may increase the oral absorption

Generic Name(s)	Significance Level	Interaction	Mechanism
			and reduce the renal secretion of digoxin. Macrolides and ketolides-related alterations in gut flora may also play a role.
Digoxin	1	Propafenone	Actual mechanism of the interaction is unknown. The volume of distribution of digoxin may be decreased along with a decrease in the renal and non-renal clearance which may increase serum digoxin levels, resulting in toxicity.
Digoxin	1	Quinidine	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Digoxin	2	Acarbose	Pharmacologic effects and plasma concentrations of digoxin may be decreased by acarbose. The mechanism of this interaction is unknown.
Digoxin	2	Aminoglycosides	Pharmacologic effects of digoxin may be increased or decreased due to altered bioavailability.
Digoxin	2	Carvedilol	Carvedilol may increase plasma concentrations and pharmacologic effects of digoxin. Although the exact mechanism is unknown, P-glycoprotein inhibition by carvedilol may enhance the absorption and decrease the renal excretion of digoxin.
Digoxin	2	Bile acid sequestrants (cholestyramine, colestipol)	Bioavailability and pharmacologic effects of digoxin may be decreased by bile acid sequestrants. The gastrointestinal absorption of digoxin may be decreased due to formation of a physical or chemical complex with bile acid sequestrants.
Digoxin	2	Diltiazem	Pharmacologic effects of digoxin may be increased by diltiazem. Elevated digoxin serum concentrations and toxicity, characterized by gastrointestinal and neuropsychiatric symptoms and cardiac arrhythmias, may occur. Pharmacodynamic effects of diltiazem and digoxin may be additive. The clearance of digoxin may be decreased by diltiazem.
Digoxin	2	Dronedarone	Plasma concentrations and pharmacologic effects of digoxin may be increased due to inhibition

Generic Name(s)	Significance Level	Interaction	Mechanism
			of P-glycoprotein (P-gP) efflux transport by dronedarone. Digoxin may also enhance the electrophysiologic effects of dronedarone.
Digoxin	2	Indomethacin	Serum concentrations and pharmacologic effects of digoxin may be increased by indomethacin. By decreasing renal blood flow, indomethacin may decrease renal elimination of digoxin.
Digoxin	2	Itraconazole	Itraconazole may increase pharmacologic effects and plasma concentrations of digoxin by decreasing renal the renal excretion of digoxin; toxicity may occur.
Digoxin	2	Penicillamine	Pharmacologic effects of digoxin may be decreased. Reduced digoxin serum levels, possibly with a suboptimal therapeutic response may result. The mechanism of this interaction is unknown.
Digoxin	2	Quinine	Quinine may increase digoxin serum concentrations. Toxicity characterized by gastrointestinal and neuromuscular symptoms, and cardiac arrhythmias may occur.
Digoxin	2	Tetracyclines	Elevated digoxin serum concentrations may occur in a small portion (<10%) of patients receiving this combination. The therapeutic and toxic effects of digoxin may be increased in these patients. The bioavailability of digoxin may be increased in some patients by tetracyclines due to an alteration in the gastrointestinal flora.
Digoxin	2	Thiazide-type diuretics	Thiazide-type diuretic-induced hypokalemia, and possibly hypomagnesemia, may increase the frequency of cardiac arrhythmias due to digoxin. Excretion of potassium and magnesium is increased by thiazide-type diuretics. Potassium and magnesium depletion can sensitize the myocardium to the toxic effects of digoxin.
Digoxin	2	Thioamines	Thioamines may alter pharmacologic effects and plasma concentrations of digoxin. The mechanism of this interaction is unknown.
Digoxin	2	Thyroid hormones	The therapeutic effectiveness of digoxin may be decreased, with

Generic Name(s)	Significance Level	Interaction	Mechanism
			possible exacerbation of cardiac arrhythmias or congestive heart failure. The mechanism of this interaction is unknown.
Digoxin	2	Verapamil	Verapamil may alter the pharmacokinetics and increase serum concentrations of digoxin. Toxicity characterized by gastrointestinal symptoms, neuropsychiatric symptoms, and cardiac arrhythmias may result.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the cardiotonic agents are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cardiotonic Agents[1-6]

Adverse Events	Digoxin
Cardiovascular	
Accelerated junctional rhythm	✔
Asystole	✔
Atrial tachycardia with or without block	✔
Atrioventricular dissociation	✔
Heart block	✔
Palpitations	<1
PR prolongation	✔
Premature ventricular contractions	✔
ST segment depression	✔
Ventricular fibrillation	✔
Ventricular tachycardia	✔
Central Nervous System	
Anxiety	✔
Apathy	✔
Asymptomatic chorea	<1
Confusion	✔
Delirium	✔
Depression	✔
Dizziness	6
Fever	✔
Hallucinations	✔
Headache	4
Mental disturbances	5
Dermatological	
Angioneurotic edema	✔
Diaphoresis	<1
Pruritus	✔
Rash	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Anorexia	✔

Adverse Events	Digoxin
Diarrhea	4
Hemorrhagic necrosis of the intestines	<1
Intestinal ischemia	<1
Nausea	4
Vomiting	2
Hematological	
Eosinophilia	<1
Thrombocytopenia	<1
Musculoskeletal	
Weakness	✔
Other	
Facial edema	✔
Gynecomastia	<1
Laryngeal edema	✔
Sexual dysfunction	<1
Vaginal cornification	<1
Visual disturbances	✔

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the cardiotonic agents are listed in Table 7. Several factors must be taken into account when dosing digoxin, including the patient's lean body weight, renal function, age, concomitant disease states, concurrent medications, and other factors that may alter the pharmacokinetic properties of digoxin.[4-5]

Table 7. Usual Dosing Regimens for the Cardiotonic Agents[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Digoxin	Atrial Fibrillation: Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Heart Failure: Rapid digitalization (oral): 500 to 750 mcg; additional doses of 125 to 375 mcg may be given cautiously at 6-8 hour intervals to achieve response. Rapid digitalization (IV): 400 to 600 mcg; additional doses of 100 to 300 mcg may be given cautiously at 6-8 hour intervals to achieve response. Gradual digitalization: 125 to 500 mcg orally or 100 to 400 mcg IV once daily	Atrial Fibrillation: Doses of digoxin used for the treatment of chronic atrial fibrillation should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects. Heart Failure: Rapid digitalization (IV): Premature: 15-25 mcg/kg Full-term: 20-30 mcg/kg 1-24 months: 30-50 mcg/kg 2-5 years: 25-35 mcg/kg 5-10 years: 15-30 mcg/kg >10 years: 8-12 mcg/kg Rapid digitalization (oral): Premature: 20-30 mcg/kg Full-term: 25-35 mcg/kg 1-24 months: 35-60 mcg/kg 2-5 years: 30-40 mcg/kg 5-10 years: 20-35 mcg/kg >10 years: 10-15 mcg/kg	Injection: 100 mcg/ml 250 mcg/ml Solution: 50 mcg/ml Tablet: 125 mcg 250 mcg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Maintenance dose (IV in divided doses): Premature: 20%-30% of IV digitalizing dose All other pediatrics: 25%-35% of IV digitalizing dose Maintenance dose (oral in divided doses): 2 to 5 years: 10-15 mcg/kg 5 to 10 years: 7-10 mcg/kg >10 years: 3-5 mcg/kg	

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Cardiotonic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atrial Fibrillation				
Hallberg et al.[17] (2007) AF group: Patients with atrial fibrillation on digoxin vs patients with atrial fibrillation not on digoxin CHF group: patients with CHF on digoxin vs patients with CHF not on digoxin AF and CHF group: Patients with atrial fibrillation and CHF on digoxin vs patients with atrial fibrillation and	Cohort AF group: ECG finding of atrial fibrillation at admission, at discharge or had a discharge diagnosis of atrial fibrillation CHF group: History of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission AF and CHF group: ECG finding of atrial fibrillation on admission, ECG finding of atrial fibrillation at discharge or a discharge diagnosis of atrial fibrillation, and a medical history of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission	N=60,764 1 year	Primary: One year mortality Secondary: Effects on LVEF, s-creatinine and AMI	Primary: Patients with atrial fibrillation who received digoxin did significantly worse than those atrial fibrillation patients who did not receive digoxin therapy (RR of death was 1.42; 95% CI, 1.29 to 1.56). Patients with CHF who received digoxin therapy did significantly worse than those CHF patients who did not receive digoxin therapy (RR of death was 1.11; 95% CI, 1.04 to 1.19). In the group of patients with atrial fibrillation and CHF, there was no mortality difference between those that received digoxin therapy and those that did not receive digoxin therapy (RR of death was 1.00; 95% CI, 0.94 to 1.06). Secondary: In patients with an LVEF of ≤30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.06; 95% CI, 0.86 to 1.31). In patients with an LVEF of >30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.14; 95% CI, 0.98 to 1.32). Regardless of level of s-creatinine (low, normal, high), there was not a significant difference in mortality between those who received digoxin therapy and those who did not: low s-creatinine (RR of death was 1.23; 95% CI, 0.91 to 1.66), normal s-creatinine (RR of death was 1.22; 95% CI, 0.94 to 1.58), high s-creatinine (RR of death was 0.98; 95% CI, 0.83 to 1.16) respectively. In patients with an AMI, the RR for death was 1.17; 95% CI, 1.10 to 1.24 between those that received digoxin therapy and those that did not receive digoxin therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
CHF not on digoxin				In patients without an AMI, the RR for death was 1.10; 95% CI, 1.04 to 1.16 between those that received digoxin therapy and those that did not receive digoxin therapy.
Khand et al.[18] (2003) Phase 1: Digoxin with placebo vs digoxin with carvedilol Phase 2: digoxin vs carvedilol	DB, PC, PG, RCT Patients with persistent atrial fibrillation for >1 month and heart failure who were receiving digoxin and diuretics	N=47 Phase 1: 4 months Phase 2: 6 months	Primary: Assessment of LVEF, ventricular rate control, symptom improvement, exercise test	Primary: Phase 1: The patients in the digoxin with carvedilol group experienced a reduction in mean ventricular rate compared to the patients in the digoxin with placebo group (65.2±15 vs 74.9±11.2 respectively; P<0.0001). The patients in the digoxin with carvedilol group experienced improved LVEF compared to the patients in the digoxin with placebo group (30±9.6 vs 26±12.4 respectively; P=0.048). The patients in the digoxin with carvedilol group experienced an improvement in symptom scores compared to the patients in the digoxin with placebo group (7 [3 to 12.5] vs 8 [3 to 15] respectively; P=0.039). The patients in the digoxin with carvedilol group experienced a reduced ventricular rate at rest and throughout steady-state exercise (peak ventricular rate 106 beats/min) compared to those patients in the digoxin with placebo group (peak ventricular rate 123 beats/min; P<0.05). Phase 2: There was no significant difference in ventricular rate control between the digoxin and the carvedilol treatment groups (88.8±18.7 vs 75.7±10.6 respectively; P=0.13). There was no significant difference in LVEF between the digoxin and the carvedilol treatment groups (21.6±11 vs 27.2±11.7 respectively; P=0.15). There was no significant difference in symptom scores between the digoxin and the carvedilol treatment groups (6 [2 to 17] vs 8 [5 to 15.5] respectively; P=0.08). There was no significant difference in ventricular rate at steady-state exercise between the digoxin and the carvedilol treatment groups.
Koh, Song et al.[19] (1995)	PRO, RCT, XO	N=37	Primary: Effects on	Primary: Patients in the digoxin plus betaxolol group experienced a significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Digoxin 0.125–0.5 mg QD plus diltiazem 90 mg BID vs digoxin 0.125–0.5 mg QD plus betaxolol QD	Patients with persistent atrial fibrillation for >1 month	7 months	ventricular rate, blood pressure, rate-pressure, maximal exercise tolerance Secondary: Safety	reduction in ventricular rates both at rest and during exercise (67±3 and 135±5 beats/min, respectively) compared to the patients in the digoxin plus diltiazem group (80±7 and 154±5 beats/min, respectively; P<0.05). Patients in the digoxin plus betaxolol group experienced a significant reduction in systolic blood pressure during maximal exercise (164±4 mm Hg) but not at rest (127±3 mm Hg) compared to the patients in the digoxin plus diltiazem group (173±4 and 130±4 mm Hg, respectively; P<0.05, P>0.05, respectively). Patients in the digoxin plus betaxolol group experienced significantly less rate-pressure products at rest (85±4 x 10^2 mm Hg/min) and during exercise (213±12 x 10^2 mm Hg/min) compared to the patients in the in digoxin plus diltiazem group (105±6 and 269±12, respectively; P<0.05 for both). Both the digoxin plus betaxolol group and the digoxin plus diltiazem group experienced a significant improvement in exercise capacity compared to baseline (P<0.05), but the groups were not statistically significant from one another (9.3±0.5 vs 9.7±0.5 MET; P>0.05). There were no statistical differences between the treatment groups in any of the efficacy points measured between time points at weeks 4 and 7 months. Secondary: No patients withdrew from the study in either treatment groups due to side effects. The digoxin plus betaxolol group experienced more side effects, which were considered minimal, compared to the digoxin plus diltiazem group. The minimal side effects observed in the digoxin plus betaxolol group included dyspnea, gastric pain, fatigue and constipation.
Hemels et al.[20] (2006) <u>Group 1:</u> Digoxin 0.125-0.25 mg QD plus acute (within 24 hours) ECV vs	MC, PRO, RCT Patients with persistent atrial fibrillation, defined as non–self-terminating arrhythmia and requiring ECV to obtain SR), and no	N=144 18 months	Primary: Freedom from permanent atrial fibrillation Secondary: Quality of life	Primary: At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent atrial fibrillation between the acute and routine ECV groups (32%; 95% CI, 22 to 44 vs 31%; 95% CI, 21 to 44, respectively; P=0.85), despite more ECVs in the acute versus the routine group ([median 3 vs 2 ECVs; P<0.05] and [≥3 ECVs in 54% vs 33% of patients, respectively; P<0.01]). At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent atrial fibrillation between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
digoxin 0.125-0.25 mg QD plus routine ECV Group 2: verapamil 120-360 mg QD with acute (within 24 hours) ECV vs verapamil 120-360 mg QD plus routine ECV Study medications were dosed to reach a target HR<100 beats/min and were administered for 4 weeks before ECV and continued during total follow-up. ECV was done one month after randomization and was only performed if anticoagulation therapy had been adequate (goal INR 2.5 to 3.5).	contraindications to anticoagulation therapy			the verapamil and digoxin groups (28%; 95% CI, 19 to 40 vs 36%; 95% CI, 25 to 48, respectively; P=0.33), despite more ECVs in the digoxin group compared to the verapamil group ([median 3 vs 2 ECVs, respectively; P<0.001] and [≥3 ECVs in 60% vs 28% of patients, respectively; P<0.001]). Secondary: At the end of the 18 month follow-up period, there were no significant differences in quality of life between the acute and the routine cardioversion groups. Also, at the end of the 18 months, there were no significant differences in quality of life between the digoxin and verapamil groups.
Heart Failure				
Koh et al.[21] (1995)	PRO, RCT	N=45	Primary: HR, blood	Primary: Resting ventricular rates were lower in all patients receiving active treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Without digoxin, diltiazem, or betaxolol (Group I) vs digoxin 0.125–0.5 mg QD (Group II) vs digoxin 0.125–0.5 mg QD and diltiazem 90 mg BID (Group III) vs digoxin 0.125–0.5 mg QD and betaxolol 20 mg QD (Group IV)	Patients with chronic heart failure for >1 month	4 weeks	pressure, rate-pressure	(groups II, III, IV) compared those patients in group I who did not receive digoxin (P<0.01). Ventricular rates during exercise were lower in groups III and IV compared to groups I and II (P<0.01). No significant differences in ventricular rate were noted between groups III and IV, either at rest or during exercise (P<0.01). Systolic blood pressure was not significantly different between the four groups (P=0.09). Rate-pressure product at rest and during exercise was significantly lower in groups III and IV compared with groups I and II (P<0.01).
DIG[22] (1997) Digoxin 0.125 to 0.5 mg once daily vs placebo Patients continued on their other CHF therapies (including diuretics and ACE	DB, MC, PC, RCT Patients ≥21 years old with heart failure and LVEF ≤45% who were in normal sinus rhythm	N=6,800 37 months	Primary: Mortality Secondary: Mortality from cardiovascular causes, death from worsening heart failure, hospitalization for worsening heart failure, and hospitalization for other causes (specifically due to	Primary: In the digoxin group, there were 1,181 (34.8%) deaths compared to 1,194 (35.1%) deaths in patients receiving placebo (95% CI, 0.91 to 1.07; P=0.80). Secondary: In the digoxin group, 1,016 (29.9%) patients died from cardiovascular compared to 1,004 (29.5%) patient deaths in the placebo group (95% CI, 0.93 to 1.10; P=0.78). There were 394 deaths in the digoxin group that were attributed to worsening heart failure compared to 449 deaths in the placebo (95% CI, 0.77 to 1.01; P=0.06). In the digoxin group, 910 patients were hospitalized for worsening heart failure compared to 1,180 patients in the placebo group (95% CI, 0.66 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitor). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.			digoxin toxicity)	0.79; P<0.001). Overall, the placebo group had a significantly higher number of patients hospitalized compared to the digoxin group, 2,184 vs 2,282 respectively (95% CI, 0.87 to 0.98; P<0.006). Other reasons for hospitalizations included cardiac events and respiratory infection. There was a statistically significantly higher number of patients in the digoxin group hospitalized for suspected digoxin toxicity compared to placebo, 67 vs 31 respectively (95% CI, 1.42 to 3.32; P<0.001).
Meyer et al.[29] (2008) Digoxin 0.125 to 0.5mg once daily vs placebo The majority of patients enrolled were also receiving diuretics and ACE inhibitors	OB Patients ≥21 years old with chronic heart failure and LVEF ≤45% who were in normal sinus rhythm (Subgroup analysis of the DIG trial[22] comparing equal numbers of patients with systolic [n=916] and diastolic heart failure [916])	N=1,832 2 to 3.2 years	Primary: Heart failure hospitalization or heart failure mortality (combined and separately) at the end of 3.2 years and 2 years of follow-up	Primary: After 3.2 years of median follow-up, the combined end point of heart failure hospitalization or heart failure mortality occurred in 28% and 32% of patients with systolic heart failure (HR, 0.85; 95% CI, 0.67 to 1.08, P=0.188) and in 20% and 25% of patients with diastolic heart failure (HR, 0.79; 95% CI, 0.60 to 1.03; P=0.085) who were receiving digoxin and placebo, respectively. After 3.2 years of median follow-up, the effect of digoxin on heart failure hospitalization was similar in patients with systolic heart failure (HR, 0.80; 95% CI, 0.62 to 1.03, P=0.079) and diastolic heart failure (HR, 0.77; 95% CI, 0.57 to 1.03, P=0.074). At the end of 2 years of follow-up, the effect of digoxin on the combined end point was similar in patients with systolic heart failure (HR, 0.72; 95% CI, 0.55 to 0.95; P=0.022) and those with diastolic heart failure (HR, 0.69; 95% CI, 0.50 to 0.95; P=0.025). At the end of 2 years of follow-up, digoxin decreased heart failure hospitalization for systolic heart failure (HR, 0.73; 95% CI, 0.54 to 0.97; P=0.033) and diastolic heart failure (HR, 0.64; 95% CI, 0.45 to 0.90; P=0.010).
Ahmed et al.[23] (2006) Digoxin 0.125-0.5 mg QD vs	MC, PC, RCT Patients with diastolic heart failure (LVEF >45%) and normal SR at baseline	N=988 37 months	Primary: Combined end point of heart failure hospitalization or heart failure mortality	Primary: At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or heart failure mortality between the digoxin group and the placebo group (102 [21%] vs 119 [24%], respectively; HR, 0.82; 95% CI, 0.63 to 1.07; P=0.136).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitor). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	This was an ancillary trial conducted in parallel with the main DIG trial.[22]		Secondary: Not prespecified, however the following outcomes were studied: all-cause and cardiovascular mortality, all-cause and cardiovascular hospitalizations, and the combined outcome of heart failure hospitalization and cardiovascular mortality	Secondary: At the end of the study, there was not a statistically significant difference in the number of all-cause deaths between the digoxin group and the placebo group (115 [23%] vs 116 [23%], respectively; HR, 0.99; 95% CI, 0.76 to 1.28; P=0.925). Also, the difference in the number of cardiovascular deaths was not significantly different between the digoxin and the placebo group (81 patients in each group; HR, 1.00; 95% CI, 0.73 to 1.36; P=0.978). At the end of the study, there was not a statistically significant difference in the number of all-cause hospitalizations between the digoxin group and the placebo group (68% vs 67%, respectively; HR, 1.03; 95% CI, 0.89 to 1.20; P=0.683). Also, the difference in the number of cardiovascular hospitalizations was not significantly different between the digoxin and the placebo group (241 [49%] vs 225 [45%], respectively; HR, 1.10; 95% CI, 0.92 to 1.32; P=0.301). At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or cardiovascular mortality between the digoxin group and the placebo group (142 [29%] vs 154 [31%], respectively; HR, 0.88; 95% CI, 0.70 to 1.11; P=0.269).
Ahmed et al.[24] (2006) Digoxin 0.125-0.5 mg QD vs placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitors) Initial dosing of	DB, MC, PC, RCT Patients with heart failure, regardless of ejection fraction, and who were in normal SR This was a post hoc analysis of a combination of the main DIG trial[22] and the ancillary DIG trial[23]	N=5,548 40 months	Primary: All-cause mortality Secondary: Mortality due to cardiovascular causes and heart failure, hospitalizations due to all causes, cardiovascular causes, and worsening heart failure	Primary: At 40 months, all cause death rate was 33% in the placebo group, 29% in the group of patients with a SDC of 0.5 to 0.9 ng/mL, and 42% in the group of patients with the SDC of ≥1.0 ng/mL (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.77; 95% CI, 0.67 to 0.89; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 1.06; 95% CI, 0.93 to 1.20; P=0.406). Secondary: At 40 months, cardiovascular mortality rate was 26% in the placebo group, 24% in the SDC of 0.5 to 0.9 ng/mL group, and 33% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.83; 95% CI, 0.71 to 0.97; P=0.019 and placebo vs SDC ≥1 ng/mL; adjusted HR, 1.07; 95% CI, 0.93 to 1.24; P=0.339). At 40 months, mortality rate due to heart failure was 12% in the placebo group, 9% in the SDC of 0.5 to 0.9 ng/mL group, and 14% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.63; 95% CI, 0.49 to 0.82; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
digoxin was based on patient's age, sex, weight and renal function.				HR, 0.87; 95% CI, 0.70 to 1.09; P=0.236). At 40 months, all cause hospitalization rates were 67% in the placebo group, 64% in the SDC of 0.5 to 0.9 ng/mL group, and 71% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.85; 95% CI, 0.78 to 0.92; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.95; 95% CI, 0.87 to 1.05; P=0.331). At 40 months, cardiovascular hospitalization rates were 53% in the placebo group, 48% in the SDC of 0.5 to 0.9 ng/mL group, and 55% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.79; 95% CI, 0.72 to 0.88; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.91; 95% CI, 0.82 to 1.01; P=0.086). At 40 months, hospitalization rates due to heart failure were 33% in the placebo group, 23% in the SDC of 0.5 to 0.9 ng/mL group, and 29% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5-0.9 ng/mL; adjusted HR, 0.62; 95% CI, 0.54 to 0.72; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.68; 95% CI, 0.59 to 0.79; P=0.086).
Uretsky et al.[25] (1993) Digoxin 0.125, 0.25, 0.375, or 0.5 mg QD vs placebo QD Digoxin was dosed to obtain a serum digoxin concentration of 0.9-2.0 ng/mL Patients continued on background therapy of diuretics.	DB, MC, PC, PG, RCT Patients ≥18 years old with NYHA Class II or III heart failure, normal SR, receiving digoxin and diuretics, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m^2	N=88 12 weeks	Primary: Treadmill time on maximal exercise testing, distance covered in a 6-minute walking test, incidence of treatment failure, time to treatment failure Secondary: Change in signs and symptoms of heart failure, MLHF questionnaire, heart failure score, 7-point GEP, LVEF, vital signs and body weight	Primary: At 12 weeks, patients in the placebo group experienced a median decline of 96 seconds in maximal exercise testing compared to a 4.5 second increase in the digoxin group (P=0.003). Digoxin did not display a significantly different effect on distance covered in a 6-minute walking test. Patients in the placebo group experienced a 39% rate of treatment failures compared to 19% in the digoxin group (P=0.039). The patients in the placebo group also experienced a decreased time to treatment failure compared to the digoxin group (P=0.037). Treatment failures included hospital admissions, increase in drug therapy and death. Secondary: At the end of the 12-week study, there was not a statistically significant difference between the placebo and digoxin groups in changes in signs and symptoms of heart failure, MLHF questionnaire or heart failure score. At the end of 12 weeks, patients in the digoxin group experienced a mean increase in LVEF by 2%±2% compared to a mean decrease in LVEF of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				3%±2% for the patients in the placebo group (P=0.016). Heart rate and body weight were significantly lower in the digoxin group compared to the patients in the placebo group (P=0.03 and P=0.044, respectively).
Packer et al.[26] (1993) Digoxin QD vs placebo QD All patients started in an 8-week, single-blind run-in period during which the doses of background therapy for heart failure were adjusted to achieve optimal clinical benefits. After the run-in period, patients were randomized to either continue receiving digoxin therapy or receive placebo. Digoxin was dosed to obtain a serum digoxin concentration of 0.9-2.0 ng/mL Patients continued on background	DB, MC, PC, RCT Patients ≥18 years old with NYHA Class II or III heart failure, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m^2, evidence of reduced exercise capacity, and normal SR, who were clinically stable while receiving digoxin, diuretics, and an ACE inhibitor	N=178 12 weeks	Primary: Rates of withdrawal from the study due to worsening heart failure, time to withdrawal, changes in exercise tolerance Secondary: Effects of discontinuing digoxin therapy on symptoms, quality of life, functional class, overall progress during the study and cardiac dimensions and function	Primary: Four patients who received digoxin, compared to 23 patients in the placebo group, withdrew from the study due to worsening of heart failure (P<0.001). The patients in the placebo group had a higher risk of worsening heart failure compared to the patients in the digoxin group over the 12-week study (RR, 5.9; 95% CI, 2.1 to 17.2; P<0.001). Exercise tolerance remained stable in patients receiving digoxin compared to deterioration in exercise tolerance in patients receiving placebo. The median difference in exercise duration between the 2 groups after 12 weeks was 42 seconds (P=0.006). Exercise endurance remained constant in patients receiving digoxin compared to a decrease in patients receiving placebo. The median difference in submaximal exercise endurance between the 2 groups after 10 weeks was 41 meters (P=0.01). Secondary: Of the patients in the placebo group, 38% experienced worsening dyspnea and fatigue compared to 16% and 18% of patients in the digoxin group (P=0.14 and P=0.04, respectively). Thirty-three percent of patients in the placebo group experienced a less of an improved quality of life compared to 47% in the digoxin group (P=0.04). Also, 48% of patients in the placebo group experienced a more frequent decline in quality of life compared to 41% in the digoxin group (P=0.04). In the placebo group, 27% of patients were reported as having a deterioration in NYHA class compared to 10% of patients in the digoxin group (P=0.019). Thirty-one percent of patients in the placebo group reported that they felt moderately worse or much worse, compared to 9% of patients in the digoxin group (P=0.007).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy of diuretics and an ACE inhibitor.				
Dhaliwal et al.[28] (2008) Digoxin, renin-angiotensin inhibition and β-blockade vs renin-angiotensin inhibition and β-blockade	RETRO Patients with a diagnosis of congestive heart failure (HF) with depressed left ventricular (LV) ejection fraction (≤45%) and who were on a regimen of rennin-angiotensin inhibitor(s) and β-blocker(s) with or without digoxin	N=347 26 months	Primary: Combined and individual rates of heart failure-related hospitalizations and total mortality	Primary: In the adjusted analysis, heart failure hospitalizations (HR, 1.08; 95% CI, 0.77 to 1.50; P=0.66), total mortality (HR, 1.03; 95% CI, 0.78 to 1.35, P=0.85), and the combined end point of heart failure hospitalization and total mortality (HR, 1.11; 95% CI 0.81 to 1.53, P=0.52) were similar between individuals who had digoxin as part of their drug regimen and those who did not. In unadjusted analyses, digoxin use was associated with a nonsignificant increase in heart failure hospitalization rates. The combined endpoint of heart failure hospitalization and total mortality and individual end points were not different between patients on digoxin therapy and those not on digoxin therapy in any of the prespecified analyses according to subgroups of ejection fraction (≤25% vs >25%), NYHA class (III or IV vs I or II), use vs nonuse of β-blockers, presence or absence of atrial fibrillation, and admission or discharge heart rates of ≤60 or ≥60 beats/minute.
Fauchier et al.[27] (2009) Digoxin vs β-blockers vs digoxin plus β-blockers vs No digoxin or β-blockers (control group)	RETRO Patients with primary or secondary diagnosis of both atrial fibrillation and heart failure between January 2000 and January 2004 were retroactively identified and followed until September 2007	N=1,269 881 days	Primary: All cause mortality	Primary: Compared with the control group (no β-blocker or digoxin), treatment with a β-blocker (RR, 0.58; P=0.005) or digoxin plus β-blocker (RR, 0.59; P=0.008) was associated with a lower risk of death. Treatment with digoxin alone was not associated with a better survival. There was a similar reduction in mortality when considered separately: heart failure patients with atrial fibrillation, association or not with coronary artery disease, and heart failure with decreased or preserved systolic function. The initial multivariate model was constructed using the predictors of all cause mortality as potential confounders. After adjustment, treatment with β-blocker alone or in combination with digoxin remained significantly associated with a better survival (RR, 0.618; P=0.04 and RR, 0.543; P=0.01, respectively). A stepwise selection technique was used to determine the final model, which included four factors associated with mortality: older age (P<0.001), decreased left ventricular ejection fraction (P=0.001), chronic renal insufficiency (P=0.007), and lack of treatment with β-blocker alone or in combination with digoxin was associated with better survival (RR, 0.618;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.04 and RR, 0.543; P=0.01).
Friberg et al.[30] (2009) Digoxin vs no digoxin	COHORT, OB Individuals treated as inpatients or outpatients for atrial fibrillation or atrial flutter	N=2,824 Mean 4.6 years	Primary: Mortality Secondary: Rates of hospitalization for heart failure, number of days at hospital for any cause, frequency of myocardial infarctions, frequency of ischemic stroke, and rate of pacemaker implantations	Primary: In the unadjusted analysis, 1,038 patients died; 412 were prescribed digoxin at index and 626 did not receive digoxin. The mortality rate was higher among individuals who were treated with digoxin (51% vs 31%, P<0.001; HR, 1.94; 95% CI, 1.71 to 2.20). When adjusted for age, gender, comorbidities and medications, the difference in mortality was not significant (HR, 1.10; 95% CI, 0.94 to 1.28). The relationship between mortality and digoxin treatment at the latest, rather than the first, contact during the observation period was also studied. Unadjusted mortality was higher among patients treated with digoxin (48% vs 31%, P<0.001); However, after multivariable adjustment, there was no difference (HR, 1.05; 95% CI, 0.92 to 1.20). When patients were matched according to their individual propensity scores, there was no difference in mortality related to digoxin use (HR, 1.05; 95% CI, 0.90 to 1.23). Secondary: Individuals treated with digoxin, who had high propensity scores for this treatment, were less often hospitalized for heart failure. The number of days in the hospital for any cause did not differ between groups. There was no difference in the frequency of myocardial infarctions or ischemic strokes related to digoxin use. There was an increased rate of pacemaker implantations among patients with digoxin as compared with those without digoxin (HR, 1.99; 95% CI, 1.16 to 3.43).
Georgiopoulou et al.[31] (2009) Digoxin (median daily dose of 0.13mg/day) vs	COHORT, RETRO Patients 18-70 years of age with advanced heart failure, LVEF ≤30% on maximum tolerated medical therapy, and NYHA	N=455 Median 27 months	Primary: Time to death, urgent transplantation, or left ventricular assist device implantation Secondary:	Primary: Death, urgent transplantation, or left ventricular assist device implantation occurred in 36.6% of patients on digoxin compared to 15.8% of patients not receiving digoxin (HR, 2.28; 95% CI, 1.51 to 3.43; P<0.001). Secondary: The composite of primary outcome plus heart failure hospitalization occurred in 63.0% of patients on digoxin compared to 40.4% of patients not receiving digoxin (HR, 1.71; 95% CI, 1.32 to 2.23; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no digoxin	Class II – IV		Composite of the primary outcome plus hospitalization for heart failure, all-cause hospitalizations, and heart failure-related hospitalizations	All-cause hospitalization rates (HR, 1.58; 95% CI, 1.18–2.13; P<0.01) and heart failure-related hospitalization rates (HR, 1.81; 95% CI, 1.17–2.80; P<0.05) were higher in patients taking digoxin compared to those who were not taking digoxin.
Siu et al.[32] (2009) Digoxin IV 0.5 mg bolus dose, followed by 0.25 mg every 8 hours vs diltiazem IV 0.25 mg/kg bolus injection over 2 minutes, followed by a second bolus of 0.35 mg/kg if ventricular rate remained >90 bpm 15 minutes later, and then a maintenance infusion at 10 mg/hr for 24 hours vs amiodarone IV loading infusion of 300 mg over the first hour, followed	RCT, OL Patients who presented to the Emergency Department with symptomatic acute atrial fibrillation for <48 hours and rapid ventricular rate (VR) >120 bpm requiring hospitalization	N=150 3 years	Primary: Sustained ventricular rate control (<90 bpm) within 24 hours Secondary: Time to VR control, sinus rhythm conversion, symptom severity, hospital stay, and adverse drug events	Primary: After the initial 24 hours, VR control was achieved in 119 of 150 patients (79%). Secondary: The median time to VR control in patients assigned to the diltiazem regimen was 3 hours (range: 1–21 hours) and was noticeably shorter than that of digoxin (6 hours, 3–15 hours) and amiodarone (7 hours, 1–18 hours) based on the log-rank test (P<0.0001). Among the patients, 45 assigned to diltiazem achieved VR control (90%), which was significantly more than among those assigned to digoxin (74%, P=0.047) and amiodarone (74%, P=0.047). Patients assigned to diltiazem had persistently the lowest mean VR after the first hour of drug administration compared with the other two groups (P<0.05). Sinus rhythm conversion rate was 31% within the first 24 hours and 38% upon discharge. There was no significant difference in sinus rhythm conversion rate among the diltiazem regimen, digoxin regimen, and amiodarone regimen within the first 24 hours (34% vs 24% vs 36%, P>0.05) and on discharge (42% vs 28% vs 44%, P>0.05). There were no differences among the three groups in the median time to sinus conversion: 5 hours (1–16 hours), 6 hours (1–19 hours), and 7 hours (1–17 hours), respectively (P>0.05). Patients receiving diltiazem had lower atrial fibrillation symptom severity scores at 24 hours compared with digoxin (P=0.047) and amiodarone (P=0.01). There was no significant difference in atrial fibrillation symptom frequency scores at 24 hours among the three groups. At 24 hours, patients receiving diltiazem had the greatest reduction in both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by 10 mg/kg over 24 hours				atrial fibrillation symptom frequency score (12.7, P=0.001) and severity score (9.8, P<0.0001) compared with those who received digoxin (8.6 and 6.1) or amiodarone (9.0 and 6.1). Patients who achieved spontaneous sinus conversion had the greatest reduction in atrial fibrillation symptom frequency score and severity score (17.2 and 11.0, respectively) compared with those who achieved VR control (9.4 and 7.7) or failed VR control (1.2 and 0.1; all, P<0.001). Among patients who remained in atrial fibrillation, those receiving diltiazem had the greatest reduction in both atrial fibrillation symptom frequency score (9.0) and severity score (7.8) in comparison with patients receiving digoxin (6.3 and 5.3, P=0.049), and patients receiving amiodarone (5.6 and 3.3, P<0.01). The mean hospital stay was 4.4 days. There was a significantly shorter hospital stay (P=0.023) in the diltiazem group (3.9 days) compared with the digoxin (4.7 days) and amiodarone groups (4.7 days). Only one patient who received amiodarone demonstrated a major adverse event with phlebitis at the intravenous access site requiring prolonged hospitalization. No bradycardia, hypotension, new-onset congestive heart failure, or myocardial infarction was observed in any of the patients.

Drug regimen abbreviations: BID=twice daily, QD=daily
Study abbreviations: CI=confidence interval, COHORT=cohort study, DB=double-blind, HR=hazard ratio, MC=multicenter, OB=observational, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SC=single center, XO=crossover
Other abbreviations: ACE inhibitor=angiotensin-converting enzyme inhibitor, AF=Atrial Fibrillation, AMI=acute myocardial infarction, CHF=congestive heart failure, DIG=Digitalis Investigation Group, ECG=electrocardiogram, ECV=electrical cardioversions, GEP=global evaluation of progress, HF=heart failure, HR=heart rate, INR=international normalized ratio, LVED=left ventricular end-diastolic, LVEF=left ventricular ejection fraction, MET=mean exercise tolerance, MLHF=Minnesota Living with Heart Failure, NYHA=New York Heart Association, SDC=serum digoxin concentration, SR=sinus rhythm

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Cardiotonic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Digoxin	injection, solution, tablet	Lanoxin®*, Lanoxin Pediatric®	$	$

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

X. Conclusions

Digoxin is the only cardiotonic agent that is currently available. It is an effective treatment option for heart failure due to its positive inotropic and neurohormonal deactivating effects. It is also beneficial for atrial arrhythmias due to its vagomimetic actions.[4-6] Digoxin injection, solution and tablets are all available in a generic formulation. Although there are minor differences with respect to pharmacokinetic parameters, all digoxin products are equally effective. Due to its potential for drug interactions and other toxicities, digoxin therapy should be monitored closely.

There are several guidelines that discuss the role of digoxin for the treatment of atrial fibrillation and heart failure. Digoxin slows atrioventricular conduction more effectively at rest than during exercise, but does not block exercise-induced tachycardia, which limits its use. For the treatment of atrial fibrillation, β-blockers and nondihydropyridine calcium channel antagonists are recommended as initial therapy to control heart rate.[9-10] Digoxin can effectively control heart rate at rest and is indicated for patients with heart failure, left ventricular

dysfunction and for sedentary individuals.[10] A combination of digoxin and either a β-blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise.[9-10] Digoxin should not be used for the pharmacologic cardioversion of atrial fibrillation. It has not been proven to be effective in preventing postoperative atrial fibrillation and is not recommended in this setting.[11-12] For the treatment of heart failure, ACE inhibitors, β-blockers and diuretics are the cornerstone of therapy.[8,13-15,33] Digoxin may be considered for patients with systolic dysfunction who have signs/symptoms of heart failure while receiving standard therapy. It has been shown to improve symptoms, exercise tolerance, quality of life and decrease hospitalizations for heart failure; however, it has no effect on survival.[8,13-15,33] Digoxin is not useful for the acute management of decompensated heart failure. The available guidelines do not give preference to one particular digoxin formulation over another.

Therefore, all brand cardiotonic agents 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 cardiotonic agent 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
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Pharmacotherapy Review of Cardiac Drugs, Miscellaneous
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I. Overview

Angina occurs when myocardial oxygen demand exceeds supply, which results in chest discomfort or pain. Common treatments for chronic angina include nitrates, β-blockers and calcium channel blockers.[5] Nitrates reduce oxygen demand by decreasing left ventricular pressure and systemic vascular resistance, as well as by dilating coronary arteries. β-blockers reduce heart rate and contractility by competitively blocking the response to beta-adrenergic stimulation in the heart. Calcium channel blockers increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction and reducing contractility. They also decrease oxygen demand by reducing systemic vascular resistance and arterial pressure.

Ranolazine is the only miscellaneous cardiac drug that is currently available and it is approved for the treatment of chronic angina. It may be used in combination with β-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, ACE inhibitors and angiotensin receptor blockers.[4] The exact mechanism of ranolazine is unknown. The anti-ischemic and antianginal effects do not depend upon reductions in heart rate or blood pressure.[4]

The miscellaneous cardiac drugs that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ranolazine is not available in a generic formulation. This class was last reviewed in May 2008.

Table 1. Cardiac Drugs, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ranolazine	sustained-release tablet	Ranexa®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous cardiac drugs are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cardiac Drugs, Miscellaneous

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement (ICSI): **Stable Coronary Artery Disease[9] (2009)**	• β-blockers should be used in all patients following a myocardial infarction based on studies showing mortality reduction. They are also the preferred first-line therapy for reducing symptoms of angina in patients with stable coronary artery disease. • If β-blockers cannot be prescribed as first-line therapy, nitrates are the preferred alternative first-line therapy because of efficacy and relatively few side effects. • For patients who are unable to take β-blockers or long-acting nitrates, the use of calcium channel blockers has been shown to be clinically effective in decreasing symptoms of angina. Calcium channel blockers have not been proven to reduce mortality. Because β-blockers have reduced mortality in the post-myocardial infarction period, they are the preferred agent for patients with stable coronary artery disease. • Combination therapy may be necessary in selected patients. A combination of β-blockers and long-acting nitrates is preferred because of efficacy and reduced potential for adverse side effects.

Clinical Guideline	Recommendation(s)
	• Ranolazine is a newly approved drug indicated for treatment of angina. Due to concerns of QT prolongation with its use, the work group can not recommend for or against its use at the current time.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina**[8] **(2007)**	• ACE inhibitors should be started and continued indefinitely in all patients with LVEF ≤40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • It is reasonable to use ACE inhibitors among lower-risk patients with mildly reduced or normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed. • Angiotensin receptor blockers are recommended for patients who have hypertension, have indications for but are intolerant of ACE inhibitors, have heart failure, or have had a myocardial infarction with LVEF ≤40%. • Angiotensin receptor blockers may be considered in combination with ACE inhibitors for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended for use in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40%, and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • The use of ranolazine for the treatment of chronic stable angina was not addressed in this guideline. • Refer to the 2002 guidelines for additional information regarding the treatment of chronic stable angina.[26]
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris**[10] **(2006)**	• ACE inhibitor therapy is indicated in patients with hypertension, heart failure, left ventricular dysfunction with or without history of prior myocardial infarction, or diabetes. • β-blockers are indicated for most patients with more than mild angina, unless contraindicated. • Short-acting nitrates may be used for prompt relief or prevention of angina, and should be offered to all patients. • Long-acting nitrates or CCBs may be considered if β-blockers are contraindicated. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. • There were no recommendations regarding the use of ranolazine for the treatment of chronic stable angina in this guideline as it was not licensed for use by the EMEA at the time it was published.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease**[12] **(2004)**	• β-blockers should be strongly considered as initial therapy, unless contraindicated. • ACEIs should be recommended for patients with symptomatic chronic stable angina to prevent myocardial infarction and death and to reduce symptoms of angina, and in patients with asymptomatic chronic stable angina with coronary artery disease, who also have diabetes mellitus, systolic dysfunction, or both. • Long-acting CCB or long-acting nitrates may be used with β-blockers if initial treatment is not successful or if β-blockers are contraindicated. • Sublingual nitroglycerin or nitroglycerin spray for immediate symptomatic relief of angina. • The use of ranolazine was not addressed in this guideline as it was published before ranolazine was approved for use in the United States.

Clinical Guideline	Recommendation(s)
American College of Cardiology (ACC)/American Heart Association (AHA): **2002 Guideline Update for the Management of Patients With Chronic Stable Angina[26] (2002)**	• Aspirin 75-325 mg should be used routinely in all patients with acute and chronic ischemic heart disease unless contraindicated. Clopidogrel may be used when aspirin is contraindicated. • β-blockers should be considered as initial therapy for chronic stable angina. • HMG-CoA reductase inhibitors should be recommended even in mild-to-moderate elevations of low-density lipoprotein cholesterol (LDL-C). • ACE inhibitors should be prescribed to patients with diabetes and/or left ventricular systolic dysfunction. • There is insufficient evidence for using an angiotensin receptor blocker in chronic stable angina. • Use sublingual nitroglycerin or nitroglycerin spray for immediate relief of angina. • Long-acting CCBs or long-acting nitrates may be used if β-blockers are contraindicated. • An immediate-release and short-acting dihydropyridine CCB can increase adverse cardiac events and should not be used. • A long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • The use of ranolazine for the treatment of angina was not addressed. This guideline was published before ranolazine was approved for use in the United States.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[7] (2007)**	<u>Early Hospital Care</u> • β-blockers should be initiated within the first 24 hours unless contraindicated. • A nondihydropyridine calcium-channel blocker (CCB) is first-line therapy in patients who have a contraindication to a β-blocker. • Immediate-release dihydropyridine CCBs may be considered in patients with UA/NSTEMI with ongoing ischemia or hypertension in the presence of adequate β-blockade. • ACE inhibitors should be administered orally to patients who do not have a contraindication within the first 24 hours to patients with congestive heart failure, diabetes, hypertension and/or left ventricular systolic dysfunction. If the patient is intolerant to an ACE inhibitor, an angiotensin receptor blocker should be administered. • At the time the patient presents with UA/NSTEMI nonsteroidal anti-inflammatory drugs, except for aspirin, should be discontinued, however β-blockers should be continued indefinitely unless contraindicated. • Ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve underlying disease. <u>Late Hospital Care, Hospital Discharge, and Posthospital Discharge Care</u> • Aspirin should be used routinely in all patients, unless contraindicated. • Clopidogrel may be used when aspirin is contraindicated or not tolerated. • Combination of aspirin and clopidogrel can be used for 12 months following UA/NSTEMI. • HMG-CoA reductase inhibitors are recommended. • Fibrates or niacin should be recommended if HDL-C is <40 mg/dL, or if triglycerides are elevated. • The use of ranolazine following discharge was not discussed in this guideline.
European Society of Cardiology: **Management of Acute**	• β-Blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia and are

Clinical Guideline	Recommendation(s)
Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-segment Elevation[11] (2007)	usually well tolerated. • Nitrates are effective for symptom relief in the acute management of anginal episodes. • CCBs provide symptom relief in patients already receiving nitrates and β-blockers; they are useful in patients with contraindications to β-blockade and in the subgroup of patients with vasospastic angina. • Nifedipine, or other dihydropyridines, should not be used unless combined with β-blockers. • It is noted that ranolazine exerts its antianginal effects by inhibiting the late sodium current and that it was not effective in reducing major cardiovascular events in Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN-TIMI) trial. • There were no recommendations regarding the use of ranolazine for the treatment of chronic stable angina in this guideline as it was not licensed for use by the EMEA at the time it was published.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous cardiac drugs 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 Cardiac Drugs, Miscellaneous[1-4]

Indication	Ranolazine
Treatment of chronic angina	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous cardiac drugs are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cardiac Drugs, Miscellaneous[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ranolazine	55	62	Intestines Liver	Renal (75) Feces (25)	7-9

V. Drug Interactions

Significant drug interactions with the miscellaneous cardiac drugs are listed in Table 5.

Table 5. Significant Drug Interactions with the Cardiac Drugs, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Ranolazine	1	Imidazoles	Azole antifungals are potent inhibitors of CYP3A and therefore may increase the steady-state plasma concentration of ranolazine, increasing the risk of dose-related prolongation in the QT interval, torsades de pointes–type arrhythmias,

Generic Name(s)	Significance Level	Interaction	Mechanism
			and sudden death.
Ranolazine	1	Macrolides and ketolides	Macrolide antibiotics inhibit the metabolism of ranolazine by the CYP3A system. Concomitant use may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	1	Nefazodone	Plasma concentrations and pharmacologic effects of ranolazine may be increased by coadministration of nefazodone. Inhibition of cytochrome P450 3A4 by nefazodone may decrease the metabolic elimination of ranolazine.
Ranolazine	1	Protease inhibitors	Protease inhibitors inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	2	Aprepitant	Plasma concentrations and pharmacologic effects of ranolazine may be increased by coadministration of aprepitant. Inhibition of cytochrome P450 3A4 by aprepitant may decrease the metabolic elimination of ranolazine.
Ranolazine	2	Barbiturates	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by barbiturates. Induction of cytochrome P450 3A isoenzymes by barbiturates may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Carbamazepine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by carbamazepine. Induction of cytochrome P450 3A isoenzymes by carbamazepine may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Diltiazem	Diltiazem inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	2	Erythromycin	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by erythromycin. Induction of cytochrome P450 3A isoenzymes by erythromycin may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Fluconazole	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by fluconazole. Induction of cytochrome P450 3A isoenzymes by fluconazole may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Hydantoins	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by hydantoins. Induction of

Generic Name(s)	Significance Level	Interaction	Mechanism
			cytochrome P450 3A isoenzymes by hydantoins may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Rifamycins	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by rifamycins. Induction of cytochrome P450 3A isoenzymes by rifamycins may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Verapamil	Verapamil inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous cardiac drugs are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cardiac Drugs, Miscellaneous[1-4]

Adverse Events	Ranolazine
Cardiovascular	
Blood pressure increased	✔
Bradycardia	≤2
Hypotension	≤2
Orthostatic hypotension	≤2
Palpitation	≤2
QT prolongation	≤1
Syncope	≤3
T-wave changes	✔
Torsades de pointes	✔
Central Nervous System	
Confusion	✔
Dizziness	5-13
Headache	3-6
Paresthesia	✔
Tremor	✔
Vertigo	≤2
Gastrointestinal	
Abdominal pain	≤2
Constipation	5-8
Nausea	4-9
Vomiting	≤2
Xerostomia	≤2
Hematologic	
Eosinophilia	✔
Hematocrit decreased	1
Leukopenia	✔
Pancytopenia	✔
Thrombocytopenia	✔
Laboratory Test Abnormalities	

Adverse Events	Ranolazine
A1C decreased	✔
BUN increased	✔
Serum creatinine increased	✔
Respiratory	
Dyspnea	≤2
Pulmonary fibrosis	✔
Other	
Angioedema	✔
Blurred vision	✔
Hematuria	✔
Hypoesthesia	✔
Peripheral edema	≤2
Renal failure	✔
Tinnitus	≤2
Weakness	✔

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous cardiac drugs are listed in Table 7.

Table 7. Usual Dosing Regimens for the Cardiac Drugs, Miscellaneous[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ranolazine	Chronic Angina: Initial, 500 mg twice daily; maximum: 1,000 mg twice daily	Safety and efficacy in children have not been established.	Tablet (SR): 500 mg 1,000 mg

SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous cardiac drugs are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Cardiac Drugs, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chaitman et al.[18] (2004) CARISA Ranolazine SR 750 to 1,000 mg BID in combination with diltiazem, atenolol, or amlodipine vs placebo in combination with diltiazem, atenolol, or amlodipine	DB, MC, PC, PG, RCT Patients with symptomatic chronic angina despite treatment with diltiazem, atenolol or amlodipine	N=823 12 weeks with long-term follow-up of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to inset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin use, survival	Primary: In the ranolazine group, exercise duration was significantly increased compared to placebo (P=0.01). Secondary: Time to angina and time to 1 mm ST-segment depression were significantly increased compared with placebo. Treatment with ranolazine significantly reduced the frequency of angina attacks (3.3 vs 2.5 attacks per week for the 750 mg group; P=0.006; and 3.3 vs 2.1 attacks per week for the 1,000 mg group; P<0.001), and nitroglycerin use compared with placebo. The most common adverse effects were constipation, dizziness, nausea, and asthenia (≤7.3% in the ranolazine group vs ≥0.7% in the placebo group). The survival rates for patients taking ranolazine were 98.4% (95% CI, 97.4% to 99.5%) at year one and 95.9% (95% CI, 94.0% to 97.7%) at year two.
Timmis et al.[22] (2006) CARISA Ranolazine SR 750 to 1,000 mg BID in combination with diltiazem, atenolol, or amlodipine vs	DB, MC, PC, RCT (Post-hoc analysis of CARISA trial) Patients with type 2 diabetes who had symptomatic chronic angina despite treatment with diltiazem, atenolol or amlodipine	N=823 12 weeks with long-term follow-up of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to onset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin usage, and A1C	Primary: In the CARISA trial, 23% of the patients were diabetic and 77% were not diabetic. The effects of ranolazine in the diabetic patients were comparable to those in the nondiabetic patients. There was no significant difference between the diabetic and nondiabetic patients in exercise duration (P=0.89), time to onset of angina (P=0.54), or time to ≥1 mm ST-segment depression (P=0.44). There was also no difference in the diabetic patients compared with the nondiabetic patients in angina frequency (P=0.81) or nitroglycerin consumption (P=0.063).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo in combination with diltiazem, atenolol, or amlodipine			levels in diabetic patients only and lipid panel as post hoc analysis	Secondary: Compared with placebo, there were significant reductions in the A1C levels in the ranolazine 750 mg (P=0.008) and ranolazine 1,000 mg (P=0.0002) treatment groups. A subgroup analysis showed that there were significant reductions in the A1C levels in insulin-dependent diabetics treated with ranolazine (P=0.016 in the 750 mg group and P=0.008 in the 1,000 mg group). The non-insulin-dependent patients in the ranolazine-treated group showed a significant reduction in A1C with the 1,000 mg dose (P=0.007), but not with the 750 mg dose (P=0.087). Treatment with ranolazine 750 mg was associated with an increase in low-density lipoprotein and total cholesterol, while treatment with ranolazine 1,000 mg did not have any effects on the lipids profile.
Stone et al.[19] (2006) ERICA Ranolazine SR 1,000 mg BID in combination with amlodipine vs placebo in combination with amlodipine	DB, PC, PG, RCT Stable patients with coronary disease and ≥3 anginal attacks per week despite maximum recommended dosage of amlodipine	N=565 6 weeks	Primary: Frequency of angina episodes per week Secondary: Average weekly nitroglycerin consumption rate, SAQ, safety as assessed by adverse events and electrocardiogram	Primary: Angina frequency at baseline averaged 5.63episodes per week. Treatment with ranolazine significantly reduced the frequency of angina episodes per week compared with placebo (2.88 vs 3.31; P=0.028). Secondary: Nitroglycerin consumption use at baseline averaged 4.72 tablets per week. Ranolazine treatment significantly reduced the use of nitroglycerin compared with placebo (2.03 vs 2.68; P=0.014). The SAQ scores on angina frequency were significantly improved in the ranolazine arm compared with placebo arm (P=0.008). There were no significant differences between treatment groups in the other SAQ measures, such as physical limitation, anginal stability, disease perception, and treatment satisfaction.
Chaitman et al.[20] (2004) MARISA Ranolazine SR 500 to 1,500 mg BID	DB, PC, RCT, XO Patients with coronary artery disease and ≥3 month history of effort angina that had previously responded to	N=191 4 weeks with long-term follow-up of up to 36 months	Primary: Exercise duration Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak,	Primary: Treatment with ranolazine at all doses resulted in significant increases in exercise duration (P<0.001). Secondary: Treatment with ranolazine at all doses resulted in significant increases in time to angina (P<0.001) and time to 1 mm ST-segment depression (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	antianginal agents. Patients discontinued anti-anginal medications prior to randomization.		exercise duration at peak, long-term survival	No clinically significant changes in heart rate or blood pressure at rest or exercise were observed. The rates of adverse events were similar for the 500 mg and placebo group, but higher with the 1,000 and 1,500 mg groups (15.6% for placebo, 16.0% for 500 mg, 21.7% for 1,000 mg, and 34.2% for 1,500 mg). The survival rates were 96.3% (95% CI, 93.0% to 99.5%) at one year and 93.6% (95% CI, 89.3% to 98.0%) at two years.
Koren et al.[25] (2007) Ranolazine SR 500 to 1,000 mg BID	MC, OL Patients with chronic angina who had completed the MARISA or CARISA trial	N=746 Mean 2.82 years	Primary: Discontinuation, adverse events, electrocardiogram findings, and mortality	Primary: 571 patients (76.7%) remained on therapy while 72 patients (9.7%) discontinued due to adverse events two years after initial dosing. There was a significant correlation between patient age >64 years and increased rates of discontinuation related to adverse events (RR, 2.32; P<0.001). A significantly lower correlation of adverse event-related discontinuation was seen in patients with a history of congestive heart failure (RR, 0.55; P=0.030). Compared to baseline, a mean prolongation of approximately 2.4 microseconds in the QT interval was observed (P<0.001). However there were no significant differences in PR or QRS intervals during this time. A total of 64 deaths (all causes) occurred during the 2,102 patient-years (3.0% annual incidence) of the study. This translates to a 97.2% and 94.4%, 1- and 2-year survival from this incidence.
Rich et al.[13] (2007) Ranolazine SR 750 to 1,000 mg BID vs placebo	MA Patients ≥70 years of age with symptomatic chronic angina despite treatment diltiazem, atenolol or amlodipine	N=1,387 (2 trials) 6 weeks	Primary: Improvement in younger patients (<70 years of age) and older patients (≥70 years of age) in exercise times, angina frequency, and adverse events	Primary: Overall ranolazine significantly improved exercise duration and time to onset of angina during exercise testing (P≤0.03). There was no difference on exercise time in younger patients compared to older patients (P>0.8). Older patients tended to have fewer angina episodes (a mean of 3.21 in the placebo group and 2.08 in the ranolazine 1,000 mg group) than younger patients (a mean of 4.16 in the placebo group and 3.11 in the ranolazine 1,000 mg group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were more commonly reported in the older patient population (32.6% in the placebo group and 44.2% in the ranolazine group) compared to the younger patients (31.2% in the placebo group and 32.1% in the ranolazine group).
Cocco et al.[23] (1992) Ranolazine IR* 10 mg, 60 mg, 120 mg or 240 mg single dose in addition to β-blocker or diltiazem vs placebo in addition to β-blocker or diltiazem	DB, MC, PC, RCT, XO Patients with chronic stable angina who remained symptomatic despite treatment with β-blockers or diltiazem	N=104 4-9 days	Primary: Exercise duration, time to angina, time to ≥1 mm ST-segment depression Secondary: Heart rate, blood pressure	Primary: Exercise duration, time to angina, and time to 1 mm ST-segment depression were significantly improved with ranolazine 240 mg dose only in the β-blocker group and the groups combined (P<0.05 for both). There was no significant difference in exercise duration, time to angina, or time to 1 mm ST-segment depression with ranolazine treatment in patients that were on the diltiazem regimen (P>0.05 for all). Secondary: Treatment with ranolazine did not result in significant changes in heart rate or blood pressure compared with placebo (P>0.05).
Pepine et al.[24] (1999) Ranolazine IR* 400 mg BID, 267 mg TID, or 400 mg TID vs placebo	DB, MC, PC, RCT, XO Patients with chronic stable angina that responded to conventional antianginal therapy	N=312 5 weeks	Primary: Time to angina onset, exercise duration, and time to 1 mm ST-segment depression at peak and trough concentrations Secondary: Safety	Primary: At peak ranolazine concentrations, time to angina onset (P≤0.02), exercise duration (P=0.013), and time to 1 mm ST-segment depression were significantly improved with all dosing regimens. At trough ranolazine concentrations, only time to 1 mm ST-segment depression was significantly improved (P=0.047). Secondary: The rates of adverse effects were similar in the ranolazine groups and placebo group. Only minor gastrointestinal adverse effects were reported more frequently with ranolazine than placebo (6.6% to 10.7% vs 3.2%).
Rousseau et al.[21] (2005) Ranolazine IR*	DB, MC, PC, XO Patients with coronary artery	N=158 7-10 days	Primary: Time to onset of angina	Primary: Treatment with ranolazine and atenolol both resulted in significant increases in time to angina, exercise duration, and time to 1 mm ST-segment depression when compared with placebo (P<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
400 mg TID for 7-10 days vs atenolol 100 mg QD for 7-10 days vs placebo for 7-10 days	disease and chronic angina who were on standard doses of atenolol		Secondary: Time to 1 mm ST-segment depression, total exercise duration, angina frequency, nitroglycerin use	Secondary: There was no significant difference between ranolazine and atenolol in the time to angina (P=0.18), time to 1 mm ST-segment depression (P=0.86), angina frequency, or nitroglycerin use. However, the increase in exercise duration was significantly greater in the ranolazine group than atenolol (mean difference of 21.1 seconds, 95% CI, 6.2 to 36.0; P=0.006).
Morrow et al.[14] (2007) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine SR 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	DB, MC, PC, RCT Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-ST-elevation myocardial infraction ≥3)	N=6,560 1 year	Primary: Composite of cardiovascular death, myocardial infarction, or recurrent ischemia Secondary: Composite of cardiovascular death, MI, or severe recurrent ischemia, rate of failure of therapy (cardiovascular death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new or worsening heart failure, or an early positive exercise tolerance test) and	Primary: The composite of cardiovascular death, myocardial infarction or recurrent ischemia occurred in 21.8% of the patients in the ranolazine group and 23.5% of patients in the placebo group (HR, 0.92; 95% CI, 0.83 to 1.02; P=0.11). Secondary: The composite of cardiovascular death, MI, or severe recurrent ischemia occurred in 18.7% of patients in the ranolazine group compared to 19.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.86 to 1.08; P=0.50). Failure of therapy occurred in 36.8% of patients in the ranolazine group and 38.3% of patients in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.02; P=0.16). Cardiovascular death occurred in 4.4% of patients in the ranolazine group and 4.5% of patients in the placebo group (HR, 1.00; 95% CI, 0.79 to 1.25; P=0.98). Myocardial infarction occurred in 7.4% of patients in the ranolazine group and 7.6% of patients in the placebo group (HR, 0.97; 95% CI, 0.81 to 1.16; P=0.76). Recurrent ischemia occurred in 13.9% of patients in the ranolazine group and 16.1% of patients in the placebo group (HR, 0.97; 95% CI, 0.76 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			safety	0.99; P=0.03). There was no difference in the documented symptomatic arrhythmias in the ranolazine group (3.0%) and the placebo group (3.1%; P=0.84).
Scirica et al.[15] (2007) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine SR 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	DB, MC, PC, RCT Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-ST-elevation myocardial infraction ≥3)	N=6,560 7 days	Primary: Incidence of clinically significant arrhythmias	Primary: Ventricular tachycardia ≥3 beats ≥100 bpm was significantly less in the ranolazine group (52.1%) compared to placebo (60.6%) (RR, 0.86; 95% CI, 0.82 to 0.90; P<0.001). Ventricular tachycardia ≥4 beats ≥100 bpm was significantly less in the ranolazine group (20.9%) compared to placebo (29.5%) (RR, 0.71; 95% CI, 0.6 to 0.78; P<0.001). Ventricular tachycardia ≥8 beats (lasting <30 seconds) was significantly less in the ranolazine group (5.3%) compared to placebo (8.3%) (RR, 0.63; 95% CI, 0.52 to 0.76; P<0.001). There was no significant difference in polymorphic ventricular tachycardia ≥8 beats in the ranolazine group (1.2%) compared to placebo (1.4%) (RR, 0.83; 95% CI, 0.54 to 1.28; P=0.40). There was no significant difference in sustained ventricular tachycardia (≥30 seconds) in the ranolazine group (0.44%) compared to placebo (0.44%) (RR, 1.01; 95% CI, 0.48 to 2.13; P=0.98). This includes monomorphic (0.13% vs 0.22%; RR, 0.59; 95% CI, 0.17 to 2.06; P=0.37) and polymorphic (0.32% vs 0.22%; RR, 1.41; 95% CI, 0.52 to 3.78; P=0.46). There was no significant difference in new-onset atrial fibrillation in the ranolazine group (1.7%) compared to placebo (2.4%) (RR, 0.74; 95% CI, 0.52 to 1.05; P=0.08). Other supraventricular arrhythmias ≥120 bpm lasting at least 4 beats were significantly less in the ranolazine group (44.7%) compared to placebo (55.0%) (RR, 0.81; 95% CI, 0.77 to 0.85; P<0.001).
Wilson et al.[17] (2009)	DB, MC, PC, RCT (Subgroup analysis	N=3,565	Primary: Time to first	Primary: The time to the first occurrence of the composite of cardiovascular death,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine SR 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	of patients with a history of prior chronic angina) Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-ST-elevation myocardial infraction ≥3)	1 year	occurrence of any element of the composite of cardiovascular death, myocardial infarction (MI), or recurrent ischemia Secondary: Anginal episodes, need for an increase or addition of any antianginal therapy, and exercise duration on treadmill or bicycle ETT performed at 8 months, safety, and incidence of clinically significant arrhythmias	MI, or recurrent ischemia was lower in patients treated with ranolazine compared with placebo among patients with prior angina (25.2% vs 29.4%, respectively, HR: 0.86; 95% CI: 0.75 to 0.97; P=0.017). This effect was due to the effects of ranolazine on recurrent ischemia. Ranolazine had no effect on the risk of cardiovascular death or MI among patients with prior angina (HR: 0.97; 95% CI: 0.80 to 1.16, P=0.71). Secondary: Ranolazine reduced the incidence of recurrent ischemia (HR: 0.78; 95% CI: 0.67 to 0.91; P=0.002), worsening angina (HR: 0.77; 95% CI: 0.59 to 1.00; P=0.048), and intensification of antianginal therapy (HR: 0.77; 95% CI: 0.64 to 0.92, P=0.005) compared to placebo among patients with prior angina. Ranolazine improved severe recurrent ischemia compared to placebo among patients with prior angina (11.9% vs 14.4%, respectively; HR: 0.81; 95% CI: 0.67 to 0.98; P=0.026). The mean number of traditional antianginal agents was decreased with ranolazine compared to placebo among patients with prior angina (2.8 vs 2.9, respectively; P=0.045). Ranolazine significantly improved all metrics of exercise performance on ETT or bicycle exercise testing compared to placebo among patients with prior angina. Ranolazine was generally well tolerated in patients with prior angina. The most common adverse effects with ranolazine compared to placebo were dizziness (12.4% vs 7.4%, respectively), nausea (9.7% vs 6.1%, respectively), and constipation (8.5% vs 3.3%, respectively). No significant increase in frequency of symptomatic documented arrhythmias was observed with ranolazine compared to placebo among patients with prior angina (risk ratio: 0.98; 95% CI: 0.67 to 1.43; P=0.92). Clinically significant arrhythmias were significantly lower in the ranolazine group (73.9% vs 83.1%, respectively; P=0.0001).
Mega et al.[16]	DB, MC, PC, RCT	N=2,291	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine SR 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	(Subgroup analysis on women) Women ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-ST-elevation myocardial infraction ≥3)	1 year	Time to first occurrence of any element of the composite of cardiovascular death, myocardial infarction (MI), or recurrent ischemia in women Secondary: Anginal episodes, incidence of clinically significant arrhythmias	Treatment with ranolazine was associated with a 29% reduction in recurrent ischemia in women compared to placebo (13.0% versus 18.2%; HR, 0.71; 95% CI, 0.57 to 0.88; P=0.002). There was no significant reduction in cardiovascular death or MI with ranolazine compared to placebo in women (P=0.80). Secondary: Treatment with ranolazine was associated with less angina compared to placebo in women (P<0.001). Fewer women treated with ranolazine needed to undergo intensification of their antianginal medical regimen compared to placebo (10.4% versus 14.4%, respectively; P=0.003). There was no difference in symptomatic documented arrhythmias in women treated with ranolazine versus placebo (2.6% versus 2.6%, respectively; P=0.95). Treatment with ranolazine was associated with fewer episodes of ventricular arrhythmias compared to placebo (P=0.008).

*The immediate-release and injectable formulations of ranolazine are not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, IR=immediate-release, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, SR=sustained-release, XO=crossover
Miscellaneous abbreviations: A1C=glycosylated hemoglobin A1c, bpm=beats per minute, CARISA=Combination Assessment of Ranolazine in Stable Angina, ERICA=Efficacy of Ranolazine in Chronic Angina, MARISA=Monotherapy Assessment of Ranolazine in Stable Angina, MERLIN-TIMI=Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes, SAQ=Seattle Angina Questionnaire, TIMI=thrombolysis in myocardial infarction

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Cardiac Drugs, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ranolazine	sustained-release tablet	Ranexa®	$$$$$	N/A

N/A=Not available

X. Conclusions

Ranolazine is the only miscellaneous cardiac drug currently available and it is approved for the treatment of chronic angina. It may be used in combination with β-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, ACE inhibitors and angiotensin receptor blockers.[4] The exact mechanism of ranolazine is unknown. The anti-ischemic and antianginal effects do not depend upon reductions in heart rate or blood pressure.[4] Ranolazine is not available in a generic formulation.

There are several organizations that provide recommendations on the treatment of chronic angina. β-blockers are considered first-line therapy for reducing symptoms of angina in patients with coronary artery disease.[8-10,12,26] Long-acting calcium channel blockers or long-acting nitrates may be used in combination with β-blockers if initial therapy is not successful, or if β-blockers are contraindicated.[8-10,12,26] The available guidelines do not provide specific recommendations regarding the use of ranolazine for the treatment of chronic angina, as it was either approved by the FDA after their publication dates or it has not been approved in their host countries.[8-10,12,26] The

ACC/AHA guideline on unstable angina and NSTEMI states that ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve the underlying disease.[7]

Three studies have evaluated the efficacy and safety of ranolazine SR in patients with chronic angina. Ranolazine (administered either as monotherapy or in combination with other anti-anginal drugs) was more effective than placebo with regards to exercise duration, time to onset of angina, frequency of angina and nitroglycerin use.[18-20] In the MERLIN-TIMI 36 trial, there was no beneficial effect on cardiovascular outcomes with ranolazine compared to placebo in patients with acute coronary syndrome.[4,14] Ventricular arrhythmias were less common with ranolazine; however, this did not lead to a reduction in mortality, arrhythmia hospitalization or arrhythmia symptoms.[4,14-15] Tolerance to ranolazine did not develop after 12 weeks of therapy.[4] Rebound increases in angina, as measured by exercise duration, have not been observed following abrupt discontinuation of ranolazine.[4]

There is insufficient evidence to support that ranolazine is safer or more efficacious than other agents commonly used for the treatment of chronic angina. Since ranolazine is not recommended as first-line therapy for the treatment of chronic angina, it should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous cardiac drugs 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 miscellaneous cardiac drug 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 Bile Acid Sequestrants
AHFS Class 240604
August 11, 2010

I. Overview

Dyslipidemia is a complex of related conditions that affects many individuals. LDL cholesterol (LDL-C) is considered the primary target of cholesterol lowering therapy. Many studies have demonstrated that elevated concentrations of LDL-C are a major risk factor for coronary heart disease, and lowering LDL-C will reduce the risk for major coronary events.[10] Non-HDL cholesterol (non-HDL-C) is a secondary target of therapy in patients with elevated triglycerides (≥200 mg/dl). This parameter takes into account the atherogenic potential associated with remnant lipoproteins in patients with hypertriglyceridemia. HDL cholesterol (HDL-C) has been shown to be an independent predictor of cardiovascular mortality and is considered an LDL modifying risk factor; however, there is insufficient data to warrant setting a specific goal for raising HDL-C.[10] The independent effect of raising HDL-C or lowering triglycerides on the risk of cardiovascular morbidity and mortality has not been determined.

The antilipemic agents are categorized into 5 different AHFS classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their FDA-approved indications, mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Bile acids are secreted into the intestines during digestion to emulsify fat and lipids to facilitate their absorption. Most of the bile acids are reabsorbed and returned to the liver via enterohepatic circulation.[4-7] The bile acid sequestrants bind to bile acids and form a complex, which is then excreted in the feces. The reduction in bile acids increases the oxidation of cholesterol to bile acids.[4-7] There is a subsequent increase in the number of LDL receptors in the liver, which increases hepatic uptake of LDL-C and reduces serum cholesterol levels. Bile acid sequestrants can decrease LDL-C by 15% to 30% and increase HDL-C by 3% to 5%.[10] Triglycerides may increase or remain unchanged.

The bile acid sequestrants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Cholestyramine (regular and light) and colestipol are available in a generic formulation. This class was last reviewed in May 2008.

Table 1. Bile Acid Sequestrants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cholestyramine and aspartame	powder for oral suspension	Questran Light®*	cholestyramine light
Cholestyramine and sucrose	powder for oral suspension	Questran®*	cholestyramine
Colesevelam	granules for oral suspension, tablet	Welchol®	none
Colestipol	granules for oral suspension, tablet	Colestid®*	colestipol

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the bile acid sequestrants are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Bile Acid Sequestrants

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[9] (2004)**	General Recommendations • Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. Heterozygous Familial Hypercholesterolemia • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins are recommended as first-line therapy (start dietary therapy simultaneously). • Bile acid sequestrants, if necessary, are recommended in combination with statins. • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid). Homozygous Familial Hypercholesterolemia • Bile acid sequestrants are not effective. Familial Defective Apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. Polygenic Hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report[10]**	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a

Clinical Guideline	Recommendation(s)
(2002)	statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Bile Acid Sequestrants • Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL-C, for younger persons with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy, and for persons needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in persons with very high LDL-C levels.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies**[11] **(2007)**	• Statins are considered first-line drugs for lowering LDL-C. • Bile acid sequestrants can serve as effective lipid-lowering alternatives. • Bile acid sequestrants tend to increase triglycerides (TG); should only be used when TG are <180 mg/dL or given in conjunction with TG-lowering agents. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.
American Heart Association (AHA)/American College of Cardiology (ACC)/National Heart, Lung, and Blood Institute (NHLBI): **Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update**[12] **(2006)**	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy.
Institute for Clinical Systems Improvement (ICSI): **Lipid Management in Adults**[13] **(2009)**	• For monotherapy, statins are the drugs of choice for lowering LDL. • If patients are unable to take statins, then bile-acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile-acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
National Institute for Health and Clinical Excellence (NICE): **Lipid Modification**[14] **(2008)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a ≥20% 10-year risk of developing CVD. • Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of CVD. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not

Clinical Guideline	Recommendation(s)
	tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of CVD. • Statin therapy is recommended for adults with clinical evidence of CVD. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dl) or LDL-C <2 mmol/L (<77 mg/dl) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association[15] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
American Heart Association (AHA)/American Stroke Association (ASA): **Primary Prevention of Ischemic Stroke[35] (2006)**	• Patients with known CAD and high-risk hypertensive patients (even with normal LDL cholesterol levels) should be treated with lifestyle measures and a statin. • For patients with low HDL-C, consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL. • For patients with elevated Lp[a], consider niacin (immediate- or extended-release formulation) in conjunction with glycemic control and LDL-C control.
American Association of the Study of Liver Disease (AASLD): **Primary Biliary Cirrhosis[36] (2009)**	• Ursodeoxycholic acid therapy is the only FDA-approved agent for the treatment of PBC. It is currently supported by the most data and is recommended for use in appropriately selected patients who have abnormal liver chemistry. • Issues of patient compliance, development of superimposed liver disease, or coadministration with bile sequestrants (e.g., cholestyramine or colestipol) should be considered for patients with suboptimal response. • Pruritus is a complication of PBC and cholestyramine is the drug of choice for the treatment of this complication. Alternative treatments of pruritus include rifampin, opioid antagonists and liver transplantation.
American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2	<u>Management of Patients With A1C Levels of 6.5% to 7.5%</u> • Monotherapy: ○ Metformin is the cornerstone of monotherapy because of its safety and efficacy. • Dual therapy:

Clinical Guideline	Recommendation(s)
Diabetes Mellitus: **An Algorithm for Glycemic Control**[34] **(2009)**	○ Metformin is the cornerstone of dual therapy. ○ The second component of the dual therapy regimen includes either an incretin mimetic, DPP-4 inhibitor, or an insulin secretagogue. ○ Additional dual therapy regimens include (1) metformin combined with colesevelam, and (2) metformin combined with an AGI. These regimens have a minimal risk of hypoglycemia and colesevelam lowers LDL cholesterol. • Insulin therapy: ○ Colesevelam is unlikely to contribute to the effectiveness of insulin. <u>Management of Patients With A1C Levels of 7.6% to 9.0%</u> • Colesevelam is not considered in this A1C range due to its limited A1C-lowering potential.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the bile acid sequestrants 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 Bile Acid Sequestrants[1-7]

Indication	Cholestyramine	Colesevelam	Colestipol
Hypercholesterolemia			
Reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated LDL cholesterol) who do not respond adequately to diet. May be useful to lower LDL cholesterol in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.	✔		
Reduction of elevated serum total and LDL cholesterol in patients with primary hypercholesterolemia (elevated LDL cholesterol) who do not respond adequately to diet			✔
Reduce elevated LDL cholesterol in adults with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with an HMG CoA reductase inhibitor (statin) as an adjunct to diet and exercise		✔	
Monotherapy or in combination with a statin to reduce LDL cholesterol levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: 1) LDL-C remains ≥190 mg/dL or LDL-C remains ≥160 mg/dL and 2) there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patient		✔	
Miscellaneous			
Improve glycemic control in adults with type 2 diabetes mellitus		✔ †	
Relief of pruritus associated with partial biliary obstruction	✔		

†Colesevelam has not been studied in type 2 diabetes as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor and has not been extensively studied in combination with thiazolidinediones.

IV. Pharmacokinetics

The pharmacokinetic parameters of the bile acid sequestrants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Bile Acid Sequestrants[1-7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Cholestyramine	0	0	None	Feces (100)	Not reported
Colesevelam	0	0	None	Feces	Not reported
Colestipol	0	0	None	Feces (100)	Not reported

V. Drug Interactions

Significant drug interactions with the bile acid sequestrants are listed in Table 5.

Table 5. Significant Drug Interactions with the Bile Acid Sequestrants[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Bile acid sequestrants (cholestyramine, colestipol)	2	Digoxin	Cholestyramine and colestipol may decrease GI absorption of digoxin, as well as alter the enterohepatic recycling of digoxin. This may result in lower systemic levels of digoxin. In addition, administering colestipol with digoxin may result in a shorter half-life of digoxin, potentially decreasing the effectiveness of digoxin.
Bile acid sequestrants (cholestyramine, colestipol)	2	Loop diuretics (furosemide)	Cholestyramine and colestipol may decrease the GI absorption of furosemide, due to binding by the anion exchange resins, resulting in lower systemic effects of furosemide. Cholestyramine and furosemide administration should be separated by as much time as possible (at least 2 hours). Colestipol should be taken as long as possible (at least 2 hours) after furosemide.
Bile acid sequestrants (cholestyramine, colesevelam)	2	Thyroid hormones	Cholestyramine and colesevelam may decrease the GI absorption of thyroid hormones by binding to them, resulting in lower systemic levels of thyroid hormones.
Cholestyramine	2	Anticoagulants	Cholestyramine may decrease the GI absorption of oral anticoagulants, resulting in lower systemic levels of anticoagulants, and potentially decreasing the effectiveness of the anticoagulant.
Cholestyramine	2	Deferasirox	Gastrointestinal absorption and enterohepatic recycling of deferasirox may be decreased due to the formation of physical chemical complexes with cholestyramine. Plasma concentrations and pharmacologic effects of

Generic Name(s)	Significance Level	Interaction	Mechanism
			deferasirox may be decreased.
Cholestyramine	2	Digitoxin	The gastrointestinal absorption and enterohepatic recycling of digitoxin are decreased due to the formation of a physical or chemical complex with cholestyramine. Pharmacologic effects of digitoxin may be decreased.
Cholestyramine	2	Leflunomide	Cholestyramine may decrease the biliary recycling of M1, the active metabolite of leflunomide.
Cholestyramine	2	Mycophenolate	Cholestyramine may bind to and impair oral absorption of mycophenolate when administered simultaneously. Cholestyramine may decrease the pharmacologic effects and plasma concentrations of mycophenolate.
Colesevelam	2	Hydantoins	Colesevelam may bind to and impair oral absorption of hydantoins and decrease the plasma concentrations of hydantoins.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the bile acid sequestrants are listed in Table 6. Cholestyramine and colestipol can decrease plasma folate levels with long-term administration; therefore, folic acid supplementation may be necessary.[4,6-7] Bile acid sequestrants may also decrease the absorption of fat-soluble vitamins A, D, E, and K.[4-7]

Table 6. Adverse Drug Events (%) Reported with the Bile Acid Sequestrants[1-7]

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Cardiovascular			
Angina	-	-	✔
Aortic stenosis	-	✔	-
Bradycardia	-	✔	-
Chest pain	-	-	✔
Hypertension	-	3	-
Myocardial infarction	-	✔	-
Tachycardia	-	-	✔
Central Nervous System			
Anxiety	✔	-	-
Dizziness	✔	-	✔
Drowsiness	✔	-	-
Fatigue	✔	4	✔
Femoral nerve pain	✔	-	-
Headache	✔	4-8	✔
Insomnia	-	-	✔
Migraine	-	-	✔
Paresthesia	✔	-	-
Syncope	✔	-	-
Tinnitus	✔	-	-
Vertigo	✔	-	-

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Weakness	-	-	✔
Gastrointestinal			
Abdominal pain/discomfort	✔	5	✔
Abdominal distention	-	✔	-
Anorexia	✔	-	✔
Bloating	✔	-	✔
Cholecystitis	-	-	✔
Cholelithiasis	✔	-	✔
Constipation	✔	9-11	✔
Diarrhea	✔	5	✔
Diverticulitis	✔	-	-
Dyspepsia	-	4-8	✔
Dysphagia	✔	-	-
Eructation	✔	-	-
Esophageal obstruction	-	✔	-
Exacerbation of hemorrhoids	-	✔	-
Fecal impaction	-	✔	-
Flatulence	✔	12	✔
GI bleeding	✔	-	-
Heartburn	✔	-	✔
Hiccups	✔	-	-
Intestinal obstruction	✔	✔	-
Malabsorption syndrome	✔	-	-
Nausea	✔	3-4	✔
Pancreatitis	✔	✔	-
Peptic ulcer	✔	-	✔
Rectal pain	✔	-	-
Sour taste	✔	-	-
Steatorrhea	✔	-	-
Vomiting	✔	2	✔
Genitourinary			
Burnt odor to urine	✔	-	-
Diuresis	✔	-	-
Dysuria	✔	-	-
Hematuria	✔	-	-
Hematological			
Anemia	✔	-	-
Hypoprothrombinemia	✔	-	-
Ecchymosis	✔	-	-
Prolonged prothrombin time	✔	-	-
Laboratory Test Abnormalities			
Creatinine phosphokinase increased	-	2	-
Hyperchloremic acidosis	✔	-	-
Hypoglycemia	-	3	-
Liver function test abnormalities	✔	✔	✔
Triglycerides increased	✔	✔	✔
Musculoskeletal			
Arthritis	✔	-	✔
Back ache	✔	-	✔
Muscle and joint pain	✔	-	✔
Myalgia	-	2	✔
Osteoporosis	✔	-	-
Respiratory			
Asthma	✔	-	-

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Cough increased	-	2	-
Dyspnea	-	-	-
Nasopharyngitis	-	3-6	-
Rhinitis	-	2-3	-
Shortness of breath	✔	-	✔
Sinusitis	-	2	-
Upper respiratory tract infection	-	5	-
Wheezing	✔	-	-
Other			
Accidental injury	-	4	-
Asthenia	-	4	✔
Back pain	-	3	✔
Dental bleeding	✔	-	-
Dental caries	✔	-	-
Dermatitis	-	-	✔
Edema	✔	-	✔
Erosion of tooth enamel	✔	-	-
Fatigue	-	-	✔
Flu syndrome	-	3	-
Increased libido	✔	-	-
Infection	-	10	-
Influenza	-	4	-
Irritation of skin, tongue, perianal area	✔	-	-
Pain	-	5	-
Urticaria	✔	-	-
Rash	✔	-	✔
Swelling of hands and feet	-	-	✔
Swollen glands	✔	-	-
Tooth discoloration	✔	-	-
Urticaria	-	-	✔
Uveitis	✔	-	-
Vitamin A deficiency	✔	-	-
Vitamin D deficiency	✔	-	-
Weight gain	✔	-	-
Weight loss	✔	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the bile acid sequestrants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Bile Acid Sequestrants[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cholestyramine	Primary Hyperlipidemia: Initial: 4 g (1 packet or scoopful) once or twice a day Maintenance: 8-16 g (2-4 packets or scoopfuls) daily divided into 2 doses; maximum, 24 g daily Pruritus Associated With	Although an optimal dosage schedule has not been established, standard texts list a usual pediatric dose of 240 mg/kg/day in 2-3 divided doses, normally not to exceed 8 g/day. The effects of long-term administration, as well as its	Powder (aspartame): 4 g Powder (sucrose): 4 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Partial Biliary Obstruction: Initial: 4 g (1 packet or scoopful) once or twice a day Maintenance: 8-16 g (2-4 packets or scoopfuls) daily divided into 2 doses; maximum, 24 g daily	effect in maintaining lowered cholesterol levels in pediatric patients are unknown.	
Colesevelam	Primary Hyperlipidemia: Tablet: 6 tablets once daily or 3 tablets twice daily with a meal and liquid Granules: 3.75 g once daily or 1.875 g twice daily Type 2 Diabetes Mellitus: Tablet: 6 tablets once daily or 3 tablets twice daily with a meal and liquid Granules: 3.75 g once daily or 1.875 g twice daily	Safety and efficacy has not been established in children <10 years of age or in premenarchal girls. Due to tablet size, the oral suspension is recommended for use in the pediatric population. Heterozygous Familial Hypercholesterolemia: Granules: 3.75 g once daily or 1.875 g twice daily	Granules: 3.75 g Tablet: 625 mg
Colestipol	Primary Hyperlipidemia: Tablets: 2-16 g per day given once or in divided doses Granules: 5 to 30 g (1-6 packets or scoopfuls) given once or in divided doses	Safety and efficacy in children have not been established.	Granules: 5 g 7.5 g Tablet: 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the bile acid sequestrants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Bile Acid Sequestrants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Ballantyne et al.[20] (2004) Cholestyramine 16 g and rosuvastatin 80 mg per day vs rosuvastatin 80 mg per day	MC, OL, PG, RCT Adults ≥18 years of age with severe hypercholesterolemia (LDL-C 190-400 mg/dL) and fasting TG <400 mg/dL	N=147 12 weeks	Primary: Percent change in LDL-C from baseline to end of treatment Secondary Percent change from baseline in LDL-C after 6 weeks of 40 mg rosuvastatin; percent change from baseline at 6 and 12 weeks of rosuvastatin treatment for: TC, HDL-C, TG, apo AI, apo B, lipid ratios (LDL:HDL) and inflammatory markers (CRP, IL6); compliance	Primary: At 12 weeks, no significant difference between the groups was seen: the rosuvastatin group had an LDL-C reduction of 56.4% and rosuvastatin with cholestyramine group had an LDL-C reduction of 60.5% (P<0.08). Secondary: LDL-C reductions were 52.2% after treatment with 40 mg rosuvastatin. Other measurements, TC, HDL-C, TG, apo B, apo AI and lipid ratios were not significantly different between the groups (P=0.20, 0.71, 0.47, 0.75, 0.53, 0.17, respectively). Decreases in CRP were 29% after 6 weeks, 42% after rosuvastatin 80 mg and 48% after rosuvastatin 80 mg with cholestyramine. 49% of patients in the cholestyramine group were not compliant with the cholestyramine treatment.
Eriksson et al.[21] (1998) Cholestyramine 16 g/day vs	MC, RCT Men and women, aged 30-65 years old	N=2,036 12 months	Primary: Reduction in LDL-C Secondary: Compliance	Primary: Percent change (CI) in LDL-C from baseline to end point was as follows: cholestyramine –26% (–23% to –29%), cholestyramine and pravastatin –36% (–33% to –39%), pravastatin (20 mg) –27% (–25% to –29%), pravastatin (40 mg) –32% (–30% to –34%). Secondary: Compliance rates with each regimen were as follows: cholestyramine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cholestyramine 8 g and pravastatin 20 mg per day vs pravastatin 20 mg per day vs pravastatin 40 mg per day				44%, cholestyramine and pravastatin 53%, pravastatin (20 mg) 76%, and pravastatin (40 mg) 78%. Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common in the cholestyramine group and the cholestyramine with pravastatin group.
Rosenson et al.[16] (2006) Colesevelam 1.5-3.75 g/day vs placebo	DB, MC, PC, RCT Hypercholesterolemia patients, LDL-C >160 mg/dL, average age of 56 years old	N=137 6 weeks	Primary: LDL particle size and LDL particle number	Primary: Mean LDL particle size increased significantly in the group receiving colesevelam 3.75 g/day (P=0.01). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.75 g/day by 13.7% (P=0.0002). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.0 g/day by 6.8% (P=0.03).
Bays et al.[17] (2006) Colesevelam 3.75 g/day vs placebo	MA Patients ≥18 years of age with LDL-C 100 mg/dL to 250 mg/dL, TG ≤300 mg/dL and on stable doses of statin therapy, either atorvastatin, pravastatin or simvastatin for ≥4 weeks	N=204 (3 trials) 6 weeks	Primary: Mean percent change in LDL-C level from baseline to end point Secondary: HsCRP, absolute and percent change in HDL-C, TC, apo AI, apo B, TG, and absolute change in HsCRP; safety (measured by incidence of	Primary: Patients receiving colesevelam with a statin had significantly greater reductions in LDL-C than those receiving placebo plus a statin at the end of the study (P<0.01 for absolute difference; P≤0.001 for % treatment difference). Secondary: HsCRP levels decreased significantly as compared to placebo when colesevelam was combined with simvastatin or pravastatin (P=0.0154 and P=0.0279, respectively). Patients receiving colesevelam with a statin did not have a significant increase in HDL-C as compared to those receiving placebo plus a statin at the end of the study (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			treatment-emergent adverse events)	Patients receiving colesevelam with a statin had significantly greater reductions in TC than those receiving placebo plus a statin at the end of the study (P<0.05). Apo B levels were not significantly different. No serious drug-related adverse events were reported. The incidence of drug-related adverse events was higher in the groups receiving colesevelam with a statin (13% to 26%) than placebo with a statin (0% to 13%).
Stein et al.[30] (2010) Colesevelam 1.875 g/day vs colesevelam 3.75g/day vs placebo	DB, PC, PG, RCT Patients 10-17 years of age with heterozygous familial hypercholesterolemia (heFH), TC >160 mg/dL who were naïve to cholesterol lowering therapy or LDL-C >130 mg/dL who were on a statin	N=194 32 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change in non-HDL-C and adverse events	Primary: Treatment with colesevelam 3.75 g/d and 1.875 g/d led to a significant reduction in LDL-C (-12.5%; P<0.001) and (-6.3%; P=0.031), respectively, compared to placebo at week 8. Reductions in LDL-C were observed for statin-naïve (-10.6%; P<0.001) or statin non-naïve patients (-20.2%; P=0.031) receiving colesevelam 3.75 g/d compared with placebo. The mean change in LDL-cholesterol was -9.3% (P<0.001) from week 8 to week 26. Those who received placebo had the greatest change in mean LDL-C (-14.5%; P<0.001), followed by patients receiving 1.875 g/d (-11.6%; P<0.001) and 3.75 g/d colesevelam (-1.9%; P=0.482). Reductions in LDL-cholesterol were also observed for statin-naïve and statin-stable patients, and patients who either changed or added a statin. Those treated with colesevelam 3.75 g/d resulted in a mean reduction from baseline in LDL-cholesterol of -14.0% (P<0.001) across all patients. Secondary: Treatment with colesevelam 3.75 g/d resulted in a reduction in TC (-7.4%; P=0.001), non-HDL-C (-10.9%; P=0.0001), apo B (-8.3%; P=0.0009), HDL-C (6.1%; P=0.008), and apo A-I (6.9%; P=0.006) at week 8. There was no significant difference in TG among the treatment groups (P=0.466). Individuals receiving colesevelam 3.75 g/d also experienced clinically significant mean reductions in TC (-8.0%; P<0.001), non-HDL-C (-11.3%; P<0.001), and apo B (-11.3%; P<0.001), clinically significant increases in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mean HDL-Cl (8.1%; P<0.001) and apo A-I (5.6%; P<0.001), and a median increase in triglycerides (11.5%; P<0.001) at week 32.
Rosenson et al.[27] (2009) Colesevelam 3.75 g/day vs placebo	DB, PC, RCT Patients with type 2 diabetes who were receiving antihyperglycemic therapy (metformin, sulfonylurea, or both)	N=65 12 weeks	Primary: Effects on atherogenic lipoprotein subclasses (LDL-P, VLDL-P, intermediate density lipoprotein [IDL-P])	Primary: Colesevelam therapy was associated with a change in A1C of −0.3% compared with a change of +0.2% in the placebo group (P=0.007). The mean percentage change in LDL-C was −9.6% in the colesevelam group compared with +2.1% in the placebo group (P=0.007). The mean percentage change in apo B was −6.3% (in the colesevelam group compared with +5.5% in the placebo group (P=0.003). There was no significant difference in TG (P=0.570) or HDL-C (P=0.585) among the treatment groups. The mean percent reduction in LDL-P was -15.5% (P=0.006) with colesevelam. The mean percent change of total atherogenic lipoproteins (LDL-P, IDL-P and VLDL-P) was reduced by -14.2% in colesevelam-treated patients (P=0.011 vs placebo).
Insull et al.[22] (2001) Colesevelam 2.3 g vs colesevelam 3.0 g vs colesevelam 3.8 g vs colesevelam 4.5 g vs	DB, MC, PC, RCT Patients with primary hypercholesterolemia, LDL-C levels between 130-220 mg/dL	N=467 32 weeks	Primary: Mean absolute change in LDL-C from baseline to the end of 24-week treatment Secondary: Mean percent change in LDL-C, mean absolute and percent change in TC, apo B, apo AI, and median absolute change and percent change in HDL-C and TG	Primary: All doses of colesevelam resulted in significant absolute and percent change decreases in LDL-C at the end point as compared to placebo (P<0.001 for all). Absolute change decreases and percent decreases in LDL-C for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 14 mg/dL (9%), 19 mg/dL (12%), 24 mg/dL (15%) and 28 mg/dL (18%). Secondary: All doses of colesevelam resulted in significant reductions of TC (P<0.001). Absolute change decreases and percent decreases in TC for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 10 mg/dL (4%), 15 mg/dL (6%), 18 mg/dL (7%) and 24 mg/dL (10%). All doses of colesevelam resulted in significant increases in HDL-C (P<0.001). Absolute changes (increases) and percent increases in TC for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 2 mg/dL (3%), 2 mg/dL (4%), 2 mg/dL (3%) and 2 mg/dL (3%). All doses of colesevelam resulted in significant reductions in apo B

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				relative to baseline (P<0.001). Changes in apo AI and lipoprotein did not result in significant changes relative to baseline, except the 2.3 g and 3.0 g doses resulted in significant changes in apo AI (P=0.02 and 0.03, respectively) TG levels did not change significantly as compared to placebo, however increases, 5% to 10%, were seen within groups from baseline to end point (P<0.05).
Hunninghake et al.[23] (2001) Colesevelam 3.8 g vs atorvastatin 10 mg vs colesevelam 3.8 g and atorvastatin 10 mg per day vs atorvastatin 80 mg per day vs placebo	DB, MC, PC, RCT Patients with elevated LDL-C levels ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change in LDL-C Secondary: Change in TC, HDL-C, TG, apo B, apo AI and lipoprotein(a) from baseline	Primary: All treatment groups resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions were –12% in the colesevelam 3.8 g group, –38% in the atorvastatin 10 mg group, –48% in the colesevelam 3.8 g and atorvastatin 10 mg group and –53% for the atorvastatin 80 mg group (P<0.05, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Secondary: Colesevelam 3.8 g/day reduced TC –6% (P<0.05), increased HDL-C 3% (P<0.05), and increased TG 10%. Atorvastatin 10 mg reduced TC –27% (P<0.0001), increased HDL-C 8% (P<0.05), and reduced TG –24% (P<0.05). Colesevelam 3.8 g and atorvastatin 10 mg reduced TC –31% (P<0.0001), increased HDL-C 11% (P<0.05), and reduced TG –1%. Atorvastatin 80 mg reduced TC –39% (P<0.0001), increased HDL-C 5% (P<0.05), and reduced TG –33% (P<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam 3.8 g with atorvastatin 10 mg. No significant differences in HDL-C were found between the groups. Apo B levels decreased significantly for all groups relative to baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.01). No significant changes in Apo AI and lipoprotein were reported.
Davidson et al.[25] (2001) Colesevelam 2.3 g vs lovastatin 10 mg vs colesevelam 2.3 g and lovastatin 10 mg taken together vs colesevelam 2.3 g and lovastatin 10 mg taken apart vs placebo	DB, MC, PC, RCT Patients with elevated LDL-C levels	N=135 4 week	Primary: Percent change in LDL-C Secondary: Changes in TC, HDL-C, TG, apo B	Primary: Colesevelam 2.3 g and lovastatin 10 mg together significantly reduced LDL-C 34% (-60 mg/dL; P<0.0001). Colesevelam 2.3 g and lovastatin 10 mg apart significantly reduced LDL-C 32% (-53 mg/dL; P<0.0001). Lovastatin 10 mg reduced LDL-C 22% (-39 mg/dL). Colesevelam 2.3 g reduced LDL-C 7% (-13 mg/dL). Both combination treatments were more effective than either treatment alone (P<0.05). Secondary: Both combination treatments resulted in reductions in TC by 21% and apo B by 24% (P<0.0001 for each). No significant effect on HDL-C or TG was found for the combination treatments.
Knapp et al.[24] (2001) Colesevelam 2.3 g vs colesevelam 3.8 g vs simvastatin 10 mg	DB, MC, PC, RCT Men and women, age 18 years and older, with elevated LDL-C levels, ≥160 mg/dL and TG ≤300 mg/dL and not taking cholesterol-lowering medication	N=258 6 weeks	Primary: Change in serum LDL-C from baseline to end point Secondary: Percent change in LDL-C, mean and percent change in TC, HDL-C, TG, apo B and apo AI	Primary: LDL-C serum changes were –7 mg/dL in the placebo group, –31 mg/dL in the colesevelam 3.8 g group, –48 mg/dL in the simvastatin 10 mg group –80 mg/dL in the colesevelam 3.8 g and simvastatin 10 mg group, –17 mg/dL in the colesevelam 2.3 g group, –61 mg/dL in the simvastatin 20 mg group and –80 mg/dL for the colesevelam 2.3 g and simvastatin 20 mg group (P<0.05, P<0.0001, P<0.0001, P<0.0001, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Secondary: LDL-C percent changes were –4% in the placebo group, –16% in the colesevelam 3.8 g group, –26% in the simvastatin 10 mg group, –42% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 20 mg vs colesevelam 3.8 g and simvastatin 10 mg vs colesevelam 2.3 g and simvastatin 20 mg vs placebo			from baseline	the colesevelam 3.8 g and simvastatin 10 mg group, –8% in the colesevelam 2.3 g group, –34% in the simvastatin 20 mg group and –42% for the colesevelam 2.3 g and simvastatin 20 mg group (P<0.05, P<0.0001, P<0.0001, P<0.0001, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Significant changes from baseline were found for all treatment groups in mean and percent change in TC (P<0.0001 for all except colesevelam 2.3 g for which P<0.05). Significant changes from baseline were found for mean and percent change in HDL-C for simvastatin 10 mg (P<0.05), colesevelam 3.8 g with simvastatin 10 mg (P<0.0001), colesevelam 2.3 g (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant changes from baseline were found for mean and percent change in TG for colesevelam 3.8 g (P<0.05), simvastatin 10 mg (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant reductions from baseline for apo B were found for all groups. Reductions were significant (P<0.05) compared to placebo for all treatment groups except colesevelam 2.3 g. Significant increases in apo AI were seen in all treatment groups except simvastatin 10 mg (P<0.05).
Primary Prevention of Cardiovascular Events				
The Lipid Research Clinics Coronary Primary Prevention Trial[18,19] (1984) Cholestyramine vs	DB, MC, RCT Asymptomatic males with primary hypercholesterolemia, following a moderate cholesterol-lowering diet	N=3,806 7.4 years average	Primary: CHD death and/or nonfatal MI Secondary: TC and LDL-C changes, incidence rates of: positive stress tests, angina, coronary bypass	Primary: The cholestyramine group had a 19% reduction in risk of CHD death or nonfatal MI compared to placebo (P<0.05). Secondary The cholestyramine group had a reduction in TC of 13.4% and a reduction in LDL-C of 20.3%. The placebo group had a TC reduction of 4.9% and a LDL reduction of 7.7%. Incidence rates of positive stress tests, angina and coronary bypass surgery

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			surgery	were decreased in the cholestyramine group by 25%, 20%, and 21%, respectively.
Type 2 Diabetes Mellitus				
Zieve et al.[26] (2007) GLOWS Colesevelam 3.75 g/day vs placebo	DB, PC, PG, PRO, RCT Patients diagnosed with type 2 diabetes, an A1C 7.0%-10.0%, and on a stable dose of a sulfonylurea and/or metformin as their only antidiabetic agent for ≥90 days	N=65 12 weeks	Primary: Change in A1C from baseline Secondary: Changes in fructosamine levels, FPG levels, postprandial glucose level, meal glucose response (difference between pre and postprandial glucose levels) % change in lipids: LDL, TC, TG, apo AI and B	Primary: The change in A1C from baseline to 12 weeks for the colesevelam group was –0.3% and for placebo +0.2%, for a treatment difference of 0.5% (P=0.007). For patients with a baseline A1C ≥8.0, there was a greater difference in A1C, –1.0%, after 12 weeks of treatment (P=0.002). The reduction in A1C in the treatment groups did not differ based on oral antidiabetic treatment. Secondary: Significantly lower FPG was seen in the colesevelam group at weeks 4 and 8, (P=0.016, P=0.011), but not at week 12. Significantly lower fructosamine levels were seen in the colesevelam group at week 12 (P=0.011). Significantly lower postprandial glucose levels were seen in the colesevelam group at week 12 (P=0.026). No significant difference was seen in meal glucose response (P=0.195). Significantly lower lipid parameters, including LDL, TC, apo B and LDL particle concentration, were seen in the colesevelam group as compared to placebo (P=0.007, P=0.019, P=0.003, and P=0.037, respectively).
Bays et al.[29] (2008) Colesevelam 3.75 g/day vs	DB, PC, PG Patients aged 18-75 years with inadequately controlled type 2 diabetes mellitus taking a stable dose of metformin	N=316 26 weeks	Primary: Mean change from baseline in A1C level Secondary: Mean change in A1C, FPG,	Primary: Colesevelam reduced mean A1C by 0.39% compared to a 0.15% increase with placebo (P<001). The treatment difference was observed as early as week 6 (P<001). Secondary: Colesevelam added to metformin monotherapy reduced A1C by -0.44% compared to an increase of 0.02% with placebo (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	monotherapy or metformin in combination with other oral anti-diabetic medications (sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and/or meglitinides)		fructosamine levels, reduction in FPG >30 mg/dL or A1C >0.7%, C-peptide, adiponectin, insulin levels, TC, LDL-C, HDL-C, non–HDL-C, TG, apo A-I, apo B, TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, apo B:apo A-I, high-sensitivity C-reactive protein (hsCRP)	Colesevelam added to metformin in combination with other oral anti-diabetic drugs reduced A1C by -0.35% compared with an increase of 0.27% with placebo (P<001). Colesevelam reduced FPG compared to placebo (−13.9 mg/dL; P=0.01), with a significant treatment difference observed at week 6 (−20.8 mg/dL; P<001). Colesevelam reduced fructosamine level compared with placebo (−23.2 µmol/L; P<0.001), with a significant treatment difference reported by 6 weeks (−25.5 µmol/L; P<0.001). Altogether, 47.7% of patients in the colesevelam group and 35.5% of patients in the placebo group experienced either a reduction in FPG >30 mg/dL or A1C >0.7% (P=0.03). A greater percentage of patients in the colesevelam group compared with placebo achieved a reduction in A1C >0.7% (38.3% vs 20.4%, respectively; P<0.001). Colesevelam did not produce a significant treatment difference for C-peptide compared to placebo (−0.1 ng/mL; P=0.54). Colesevelam was not associated with a significant treatment difference in adiponectin (−0.3 µg/mL; P=0.52), insulin (−0.9 µIU/mL; P=0.51), or the HOMA index (−0.3; P=0.68). Compared with placebo, colesevelam reduced LDL-C, TC, non–HDL-C, and apo B levels (all P<0.001). There was no significant difference in HDL-C, TG or apo A-I between the treatment groups. Treatment with colesevelam led to a greater reduction in hsCRP compared to placebo (−14.4%; P=0.02).
Fonseca et al.[28] (2008) Colesevelam 3.75 g/day	DB, PC, PG Adults with type 2 diabetes mellitus that were inadequately	N=461 26 weeks	Primary: Mean change in A1C Secondary:	Primary: Colesevelam reduced A1C by -0.32%, whereas placebo increased A1C by 0.23% (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	controlled on a stable dose of sulfonylurea alone or in combination with additional oral antidiabetes agents for at least 90 days		FPG, fructosamine, C-peptide, mean change in A1C for the sulfonylurea monotherapy and sulfonylurea combination therapy cohorts; percentage of patients achieving a reduction in FPG ≥30 mg/dl or A1C ≥0.7%; lipids, lipoproteins, and lipid and lipoprotein ratios; high-sensitivity C-reactive protein (hsCRP)	Colesevelam significantly lowered FPG compared to placebo (-13.5 mg/dl; P<0.009), with a difference observed as early as 6 weeks (-13.7 mg/dl; P<0.001). A significant difference in fructosamine was reported with colesevelam compared to placebo (-21.4 µmol/l; P<0.001). There was no significant difference in C-peptide among the treatment groups (P=0.102). A similar effect on A1C was observed in the sulfonylurea monotherapy group (-0.79%; P<0.001) and the sulfonylurea combination therapy (-0.42%; P<0.001) groups. A significantly greater percentage of patients in the colesevelam group achieved an A1C reduction ≥0.7% compared with placebo (35.2% vs 16.5%, respectively; P<0.001). There was a significantly greater number of individuals in the colesevelam group who achieved either a reduction in A1C ≥0.7% or a reduction in FPG ≥30 mg/dl compared to placebo (47.5% vs 32.1%, respectively; P=0.001). Significant treatment differences in LDL-C, non–HDL-C, TG, TC, TG, apo A-I, and apo B were observed after 26 weeks of treatment with colesevelam compared to placebo (P<0.001 for all). The LS mean percent change in LDL cholesterol from baseline to week 26 (LOCF) was -16.1% in the colesevelam group and +0.6% in the placebo group (-16.7%; P<0.001). There was no significant difference in HDL-C among the treatment groups (P=0.916). Significant treatment differences between colesevelam and placebo were reported in TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, and apo B:apo A-I (all P≤0.003). There was no significant difference in hsCRP among the treatment groups (P=0.063).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Goldberg et al.[32] (2008) Colesevelam 3.75 g/day vs placebo	PRO, MC, DB, PC, PG Patients 18 to 75 years of age with type 2 diabetes not adequately controlled with insulin alone or in combination with oral antidiabetes agents (a biguanide, a biguanide sulfonylurea combination, a sulfonylurea, a thiazolidinedione, or a meglitinide)	N=287 16 Weeks	Primary: Mean change in A1C Secondary: FPG, fructosamine, A1C, percentage of patients achieving a reduction in FPG ≥30 mg/dl or A1C ≥0.7%, C-peptide, TC, LDL-C, HDL-C, non–HDL-C, TG, apo A-I, apo B, TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, apo B:apo A-I, high-sensitivity C-reactive protein	Primary: The mean change in the A1C was −0.41% in the colesevelam group and 0.09% in the placebo group (P<.001). Secondary: There was no significant difference in FPG among the treatment groups (P=0.08). Colesevelam significantly decreased mean fructosamine levels compared with placebo (P<0.001). Approximately 48.6% of patients in the colesevelam group and 31.6% of patients in the placebo group had a reduction in the FPG level >30 mg/dL or a reduction in the A1C of >0.7% (P=0.004). More than twice as many patients in the colesevelam-treated group had a reduction in the A1C level of 0.7% or greater compared with those in the placebo group (34.7% vs 14.0%; P<001). However, no significant difference was noted in the percentage of individuals achieving a reduction in FPG level of 30 mg/dL or higher between the colesevelam treated and placebo groups at week 16. Mean change from baseline in C-peptide levels was similar in both groups. No significant LS mean treatment difference was evident at week 16 LOCF (P=0.65). Colesevelam resulted in a significantly greater percentage reduction in LDL-C compared to placebo (P<0.001). The median percent change and median change in triglycerides for the colesevelam and placebo groups were 22.7% vs 0.3% and 32.0 mg/dL vs −1.3 mg/dL, respectively (P<0.001 for both). Treatment with colesevelam significantly reduced apo B levels by 5.3% compared with placebo (P=0.04), but did not result in a significant increase in apo A-I. Colesevelam led to a significant decrease in LDL-C:HDL-C and apo B:apo A-I, but not in the TC:HDL-C or non–HDL-C:HDL-C. There was no significant difference in hsCRP among the treatment groups (P=0.13).
Goldfine et al.[33] (2010)	OL, ES	N=509	Primary: Safety and	Primary: During the extension, 70.9% of patients experienced an adverse event. The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Colesevelam 3.75 g/day vs placebo	Patients 18 to 75 years of age with type 2 diabetes who were inadequately controlled on insulin-based therapy, metformin-based therapy or sulfonylurea-based therapy	52 weeks	tolerability Secondary: Change in A1C and FPG, percent change in lipid and lipoprotein levels, change in lipid ratios, percentage of patients who achieved either a reduction in A1C ≥0.7% or FPG ≥30 mg/dL, percentage of patients who achieved A1C <7.0%	majority (88.1%) were mild or moderate in severity. Fifty-six patients (11%) experienced a drug-related adverse event. Most drug-related adverse events were gastrointestinal (constipation and flatulence) in nature. Thirty–five (6.9%) discontinued use due to an adverse event; 16 patients (3.1%) discontinued due to a drug-related adverse event. Fifty-four patients (10.6%) had a serious adverse drug reaction; only one was considered to be drug related; 12 patients (2.4%) discontinued the drug due to a serious event. Seventeen patients (3.3%) reported an episode of hypoglycemia; most were considered mild and two were considered moderate severity. Secondary: Treatment with colesevelam reduced the A1C by -0.6% compared to -0.1% with placebo. At week 52, 14.1% of patients achieved A1C <7.0% and 26.9% of patients had a reduction in A1C of ≥0.7%. One-hundred-twenty-six patients (24.8%) achieved a reduction in FPG ≥30 mg/dl from baseline A at 52 weeks. Improvements in mean LDL-C with colesevelam were maintained. Both groups that received colesevelam had sustained effects over time. Baseline A had lipid and lipoprotein levels were nearly the same between colesevelam and placebo. By the conclusion of the double-masked study (baseline B), the individuals that received colesevelam had reduced mean levels of LDL-C, non-HDL-C, TC, and apo B, and increased mean levels of HDL-C, median levels of TG, and mean levels of apo A-I relative to baseline (baseline A). For those who received colesevelam in the double-masked study, the lipid effects were maintained through the extension. For those who received colesevelam in the 52-week extension, mean LDL-C, non-HDL-C, TC and apo B levels decreased while mean HDL-C, median TG, and mean apo A-I levels increased.
Jialal et al.[31] (2009) Colesevelam 3.75g/day	RCT, DB, PC (Pooled analysis of 3 trials) Patients 18 to 75 years	N=1,018 16 to 26 weeks	Primary: Glycemic and lipid effects Secondary:	Primary: Mean A1C was significantly reduced with colesevelam compared to placebo (−0.54%; P<0.0001). Mean FPG was significantly reduced with colesevelam versus placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	of age with type 2 diabetes who were inadequately controlled on insulin-based therapy, metformin-based therapy or sulfonylurea-based therapy		Lipid effects on those patients on concomitant statin treatment	(−15.1 mg/dL; P<0.0001). Colesevelam therapy resulted in a significant reduction in TC and LDL-C compared with placebo (−5.15% and −15.3%, respectively; P<0.0001). TG was significantly increased in the colesevelam group relative to placebo (15.0%; P<0.0001). Non-HDL-C and apo B were reduced with colesevelam versus placebo (−6.80% and −6.6%, respectively; P<0.0001). There was no significant effect on HDL-C between the two groups. Apo A-I levels increased significantly in the colesevelam group relative to placebo (2.8%; P<0.0001). Median levels of high-sensitivity C-reactive protein (hsCRP) were significantly reduced with colesevelam relative to placebo treatment (−0.4 mg/L; P=0.0009). Secondary: Colesevelam treatment resulted in a significant decrease in A1C (-0.45%; P<0.0001) and LDL-C (-15.6%; P<0.0001) in patients on statin therapy at baseline.

Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial
Miscellaneous abbreviations: A1C=glycosylated hemoglobin, apo=apolipoprotein, CHD=coronary heart disease, CRP=C-reactive protein, FPG=fasting plasma glucose, GLOWS=Glucose-Lowering Effect Of Welchol, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, hsCRP=high-sensitivity C-reactive protein, IL6=interleukin 6, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, MI=myocardial infarction, TC=total cholesterol, TG=triglycerides

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Bile Acid Sequestrants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cholestyramine and aspartame	powder for oral suspension	Questran Light®*	$$$-$$$$	$$-$$$
Cholestyramine and sucrose	powder for oral suspension	Questran®*	$$-$$$$	$$
Colesevelam	granules for oral suspension, tablet	Welchol®	$$$$-$$$$$	N/A
Colestipol	granules for oral suspension, tablet	Colestid®*	$$$	$$

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

X. Conclusions

The bile acid sequestrants are approved as an adjunct to diet and exercise to reduce total and LDL cholesterol.[1-7] In addition, cholestyramine is indicated to relieve pruritus associated with partial biliary obstruction. Colesevelam is also indicated for the treatment of type 2 diabetes mellitus. Bile acid sequestrants can lower LDL-C by 15% to 30% and raise HDL-C by 3% to 5%.[9] Serum triglyceride levels may increase or remain unchanged. Cholestyramine (regular and light) and colestipol are available in a generic formulation.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes (TLC).[9-14] For patients who cannot achieve LDL-C goals with the use of a statin alone, the addition of another LDL-C lowering drug such as niacin, a bile acid sequestrant or ezetimibe is recommended. For the treatment of type 2 diabetes, metformin is recommended as first-line therapy due to its efficacy and safety. According to the AACE/ACE algorithm, an incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin.[34] The combination of metformin and colesevelam is considered an alternative treatment option. This regimen has a minimal risk of hypoglycemia and colesevelam also lowers LDL-C.[34] Pruritus is a complication of primary biliary cirrhosis and cholestyramine is the drug of choice for the treatment of this complication.[36] Guidelines do not give preference to one bile acid sequestrant over another.

Clinical trials have demonstrated that the bile acid sequestrants can effectively lower LDL-C, non-HDL-C, total cholesterol and positively impact other lipid/lipoprotein parameters.[16-33] There are very few trials that directly compare the efficacy and safety of these agents. Treatment with cholestyramine led to a 19% reduction in the risk of fatal and non-fatal myocardial infarction in the Lipid Research Clinics Coronary Primary Prevention Trial (LRD-CPPT).[18-19] Positive cardiovascular outcomes have also been detected in clinical trials which combined bile acid sequestrants with other lipid-modifying drugs.[10] The efficacy of colesevelam as monotherapy for the treatment of type 2 diabetes has not been assessed.[5] When added to existing diabetic regimens, colesevelam lowered the A1C by 0.3% to 0.6% compared to the addition of placebo.[26,28-29,31-33]

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

Therefore, all brand bile acid sequestrants 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 bile acid sequestrant 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 Cholesterol Absorption Inhibitors
AHFS Class 240605
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I. Overview

The antilipemic agents are categorized into 5 different AHFS classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their FDA-approved indications, mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Ezetimibe is the only cholesterol absorption inhibitor that is currently available. It inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver.[4] This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe can lower LDL cholesterol by about 18%.

The cholesterol absorption inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ezetimibe is not available in a generic formulation. This class was last reviewed in May 2008.

Table 1. Cholesterol Absorption Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ezetimibe	tablet	Zetia®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cholesterol absorption inhibitors are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Cholesterol Absorption Inhibitors

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[5] (2004)**	General Recommendations • Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. Familial Defective Apolipoprotein B-100 (FDB)

Clinical Guideline	Recommendation(s)
	• TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. Polygenic Hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report**[6] **(2002)**	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Cholesterol Absorption Inhibitors • Cholesterol absorption inhibitors (e.g., ezetimibe) are not mentioned in this guideline.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies**[7] **(2007)**	• Statins are considered first-line drugs for lowering LDL-C. • As monotherapy, cholesterol absorption inhibitors have mild LDL-lowering effects and can be used for patients with active liver disease, having adverse effects on statins or when statins, fibrates and nicotinic acid are contraindicated. • Their primary role in therapy is in combination with statins. • Cholesterol absorption inhibitors have not been shown in clinical trials to reduce myocardial infarction and coronary death. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update**[8] **(2006)**	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Lipid Management in Adults**[9] **(2009)**	• For monotherapy, statins are the drugs of choice for lowering LDL. • If patients are unable to take statins, then bile-acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it.

Clinical Guideline	Recommendation(s)
	• Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile-acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
National Institute for Health and Clinical Excellence (NICE): **Lipid Modification[10] (2008)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a ≥20% 10-year risk of developing CVD. • Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of CVD. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of CVD. • Statin therapy is recommended for adults with clinical evidence of CVD. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dl) or LDL-C <2 mmol/L (<77 mg/dl) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association[54] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
American Heart Association (AHA)/American Stroke Association (ASA): **Primary Prevention of Ischemic Stroke[41] (2006)**	• Patients with known CAD and high-risk hypertensive patients (even with normal LDL cholesterol levels) should be treated with lifestyle measures and a statin. • For patients with low HDL-C, consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL. • For patients with elevated Lp[a], consider niacin (immediate- or extended-release formulation) in conjunction with glycemic control and LDL-C control.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cholesterol absorption 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 Cholesterol Absorption Inhibitors[4]

Indication	Ezetimibe
Adjunctive therapy to diet for the reduction of elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B) in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia when administered as monotherapy or in combination with an HMG-CoA reductase inhibitor	✔
Adjunctive therapy to diet for the reduction of elevated TC, LDL-C, apo B, and non-high-density lipoprotein cholesterol (non–HDL-C) in patients with mixed hyperlipidemia when administered in combination with fenofibrate	✔
Adjunct to other lipid-lowering treatments (e.g., low-density lipoprotein apheresis) or if such treatments are unavailable for the reduction of elevated TC and LDL-C levels in patients with homozygous familial hypercholesterolemia when administered in combination with atorvastatin or simvastatin	✔
Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the cholesterol absorption inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cholesterol Absorption Inhibitors[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism	Excretion (%)	Half-Life (hours)
Ezetimibe	Not reported	>90	Intestine, extensive Liver	Renal (11) Feces (78)	19-30

V. Drug Interactions

Significant drug interactions with the cholesterol absorption inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Cholesterol Absorption Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Ezetimibe	2	Cyclosporine	Although the mechanism is unknown, when cyclosporine and ezetimibe are administered concomitantly exposure to both drugs may be increased, potentially increasing the pharmacologic effects and adverse reactions.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the cholesterol absorption inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cholesterol Absorption Inhibitors[1-4]

Adverse Events	Ezetimibe
Central Nervous System	
Depression	✔
Dizziness	✔
Fatigue	2
Headache	✔
Paresthesia	✔
Dermatologic	
Erythema multiforme	✔
Rash	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Diarrhea	3-4
Nausea	✔
Hematologic	
Thrombocytopenia	✔
Laboratory Test Abnormalities	
Creatine phosphokinase increased	✔
Liver transaminases increased	1
Musculoskeletal	
Arthralgia	3
Myalgia	3
Myopathy	✔
Pain in extremities	3
Rhabdomyolysis	✔
Respiratory	
Coughing	2.3
Nasopharyngitis	4
Sinusitis	3
Upper respiratory tract infection	3-4
Other	
Anaphylaxis	✔
Angioedema	✔
Cholecystitis	✔
Cholelithiasis	✔
Hepatitis	✔
Hypersensitivity reactions	✔
Influenza	2
Pancreatitis	✔

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the cholesterol absorption inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Cholesterol Absorption Inhibitors[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ezetimibe	Homozygous Familial Hypercholesterolemia: 10 mg once daily Homozygous Sitosterolemia: 10 mg once daily Mixed Hyperlipidemia: Monotherapy: 10 mg once daily Combination therapy with fenofibrate: 10 mg once daily Primary Hypercholesterolemia: Monotherapy: 10 mg once daily Combination therapy with a statin: 10 mg once daily	Safety and efficacy in children <10 years of age have not been established. Heterozygous Familial Hypercholesterolemia: 10 mg once daily	Tablet: 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cholesterol absorption inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Cholesterol Absorption Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Dujovne et al.[12] (2002) Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)	N=892 12 weeks	Primary: Percent change from baseline to end point in plasma concentration of direct LDL-C Secondary: Changes and percent changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, and HDL-C at end point, changes from baseline HDL_2-C and HDL_3-C, apo AI, apo B, Lp(a) at end point, adverse events	Primary: The ezetimibe group achieved a mean percent reduction from baseline to end point in the plasma concentration of LDL-C of 16.9% compared to 0.4% in the placebo group (P<0.01). Secondary: There was a –17.68% compared to a 1.11% change in the calculated LDL-C from baseline in the ezetimibe and placebo groups, respectively (P<0.01). Ezetimibe also significantly decreased the apo B, TC, and TG as well as significantly increased HDL-C and HDL_3-C from baseline (P<0.01). However, there was no significant change in HDL_2-C and apo AI with ezetimibe compared to placebo (P=0.76 and P=0.50, respectively). Treatment-emergent adverse events occurred in 66% of patients taking ezetimibe and 63% of patients taking placebo. The most commonly reported adverse event in both treatment groups were upper respiratory tract infections and headache. The adverse events were considered to be mild to moderate and were similar between treatment groups.
Knopp et al.[13] (2003) Ezetimibe 10 mg QD vs	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and TG	N=827 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of direct LDL-C	Primary: The mean plasma concentration of direct LDL-C from baseline to end point was 17.7% in the ezetimibe group compared to 0.8% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased calculated LDL-C, apo B, TC and Lp(a) and significantly increased HDL-C and HDL_2-C (P≤0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	≤350 mg/dL)		Secondary: Changes and percentage changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, HDL-C at end point, HDL_2-C, HDL_3-C, apo AI, apo B, Lp(a), adverse events	However, the change in HDL_3-C, apo AI, and TG from baseline did not result in significant differences between treatment groups (P=0.49, P=0.27, P=0.09). The percentage of patients reporting treatment-emergent adverse events was 61% in the ezetimibe group and 65% in the placebo group. No individual adverse event was prevalent in either group and all were considered mild to moderate in severity. Overall, the adverse event profiles were similar between both treatment groups.
Knopp et al.[14] (2003) Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Pooled data of men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)	N=1,719 (2 trials) 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of LDL-C Secondary: Percentage change from baseline in TC, TG, HDL-C, HDL2-C, HDL3-C, apo AI, apo B, Lp(a), adverse events	Primary: In the pooled analysis, LDL-C was reduced by a mean 18.2% from baseline in the ezetimibe group compared to an increase of 0.9% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased TC, apo B, Lp(a), and TG and increased HDL-C compared to placebo (P<0.01). However, there were no statistically significant differences in the change of HDL_2-C, HDL_3-C and apo AI between ezetimibe and placebo (P=0.08, P=0.06, and P=0.26). The overall adverse event profiles were similar between the ezetimibe and placebo groups. Approximately 62% of patients in the ezetimibe group and 62% of patients in the placebo group reported adverse events. Also, there were no significant between-group differences in the laboratory or clinical safety parameters or gastrointestinal, liver, or muscle side effects.
Wierzbicki et al.[15] (2005) Ezetimibe 10 mg QD vs placebo	PRO Patients with refractory familial hyperlipidemia or intolerance to statin therapy	N=200 Not reported	Primary: LDL-C, TG, HDL-C, CRP, ALT	Primary: Ezetimibe was associated with 7% reductions in LDL-C and 11% reductions in apo B. The proportion of patients achieving LDL-C <3 mmol/L increased from 6% to 18%. There were no significant differences in TG, HDL-C, CRP, or ALT.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kalogirou et al.[16] (2007) Ezetimibe 10 mg QD vs placebo	PRO Patients with primary dyslipidemia and no evidence of CHD, average 54 years of age, average BMI of 26.9 kg/m^2	N=50 16 weeks	Primary: Lipoprotein subfractions	Primary: A significant median reduction in serum HDL-C concentration from 1.5 mmol/L (1.1 to 2.6) at baseline to 1.4 mmol/L (0.9 to 2.6) posttreatment was observed with ezetimibe treatment. The median change in HDL-C was –6.6% (P<0.001). A significant median reduction in TC from 7.1 mmol/L (4.9 to 11.1) at baseline to 5.8 mmol/L (4.3 to 8.9) posttreatment was observed with ezetimibe treatment. The median change in TC was –15.5% (–34.5% to 4.2%) with ezetimibe treatment (P<0.001 vs placebo). Mean serum TG decreased from 1.5 mmol/L (0.6 to 4.28) at baseline to 1.4 mmol/L (0.6 to 3.2) posttreatment; a median percent change of 9.3% (–32.4% to 15.7%; P<0.05). Mean serum LDL-C levels significantly decreased from 3.8 mmol/L (2.5 to 7.3) at baseline to 3.2 mmol/L (1.8 to 5.4) posttreatment; a median percent change of –20.1% (–51.1% to 23.1%; P<0.001).
Gonzalez-Ortiz et al.[17] (2006) Ezetimibe 10 mg QD vs placebo	DB, PC, RCT Obese, dyslipidemic patients 18-45 years old	N=12 90 days	Primary: TC, LDL-C Secondary: HDL-C, TG, VLDL	Primary: Ezetimibe-treated patients compared with placebo-treated patients had decreased TC (6.0 vs 4.2 mmol/L; P=0.011) and LDL-C (4.0 vs 2.2 mmol/L; P=0.003) without affecting insulin sensitivity. Secondary: There were no differences in HDL-C, TG, and VLDL (P=not significant).
Pearson et al.[22] (2005) Ezetimibe 10 mg QD vs placebo Patients in both groups continued	MC, DB, PC, PG Hypercholesterolemic patients ≥18 years of age with LDL-C levels exceeding NCEP ATP III goals while taking a stable, approved dose of any statin, following a cholesterol-lowering diet for at least 6 weeks	N=3,030 6 weeks	Primary: Percent reduction in LDL-C level from baseline after 6 weeks of double-blind treatment Secondary: Percentage of patients who achieved NCEP ATP III target	Primary: Ezetimibe added to a statin significantly reduced mean LDL-C levels by an additional 25.8% compared with a reduction of 2.7% with the addition of placebo to statin (95% CI, –24.4% to –21.7%; P<0.001). Secondary: The addition of ezetimibe to statin resulted in an additional 23.8% to 25.7% reduction in LDL-C in all NCEP ATP III risk categories. Treatment differences were –24.0%, –19.7%, and –19.9% in the CHD or CHD risk equivalent, multiple risk factors, or <2 risk factors groups, respectively (P<0.001 ezetimibe vs placebo for each risk category). No significant differences were found according to age, sex, or race category (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to receive their current dose of statin therapy.			LDL-C levels in the total population and by NCEP ATP III risk categories	
Pearson et al.[19] (2006) Ezetimibe 10 mg QD Patients either received ezetimibe as monotherapy, in combination with a low-dose statin (20 mg/day or less of atorvastatin or its equivalent), or in combination with a high-dose statin (20 mg/day or more of atorvastatin or its equivalent).	RETRO Cohort Men and women ≥18 years old who took ezetimibe for a minimum of two weeks	N=84 2-6 weeks	Primary: Change in fasting lipid profile at baseline to 2-6 weeks of ezetimibe therapy, clinical effectiveness results stratified by primary versus secondary prevention Secondary: Percentage of patients able to achieve their LDL-C target levels in accordance with their calculated Framingham risk category and defined Canadian guidelines and safety and tolerability	Primary: The mean reductions from baseline to 2-6 weeks of ezetimibe therapy were: TC 1.11mmol/L (16.5%), LDL-C level 1.01 mmol/L (22.3%), and ratio of TC:HDL 0.68 mmol/L (12.8%) (all P<0.001). The HDL-C level increased by 0.06 mmol/L (4.6%) from baseline to 2-6 weeks of ezetimibe therapy (P<0.001). Results were similar when stratified by primary (N=28) versus secondary (N=56) prevention. Among the primary prevention group, only the TC levels, LDL-C levels and TC:HDL ratio reductions were statistically significant (P<0.001). In the secondary prevention group, the reductions in TC levels, LDL-C levels, HDL-C levels and TC:HDL ratio all achieved statistical significance (P<0.001). LDL-C level reductions from baseline, stratified by drug regimen, were –1.03 mmol/L (–20.5%) for ezetimibe monotherapy, –1.19 mmol/L (–30.1%) for ezetimibe and a low-dose statin, and –0.95 mmol/L (–22.5%) for ezetimibe plus a high-dose statin (P<0.001 for ezetimibe monotherapy and ezetimibe plus a high-dose statin; P=0.0017 for ezetimibe plus a low-dose statin). Secondary: There were 7 patients out of 34 (20.6%) in the ezetimibe monotherapy group, 5 out of 12 (41.6%) in the ezetimibe plus low-dose statin group and 18 out of 38 (47.4%) in the ezetimibe plus high-dose statin group who achieved previously unattainable target LDL-C levels. There were 4 patients who discontinued therapy due to treatment-related adverse event.
Coll et al.[31] (2006) Ezetimibe 10 mg QD	RCT HIV patients, ≥6 months on stable HAART, ≥18 years of age, fasting LDL ≥3.30	N=20 6 weeks	Primary: LDL-C, TC, endothelial function	Primary: Ezetimibe-treated patients experienced a 20% (P=0.002) LDL-C reduction and a 10% TC reduction (P=0.003). Fluvastatin-treated patients experienced a 24% LDL-C reduction (P=0.02) and a 17% TC reduction (P=0.06).

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vs fluvastatin XR 80 mg QD	mmol/L			There were no significant differences in lipid-lowering ability between groups. Ezetimibe-treated patients did not experience significant changes in endothelial function. Fluvastatin-treated patients experienced an increase in the rate of endothelial function by 11% (P=0.5).
Bays et al.[38] (2006) Ezetimibe 10 mg and colesevelam 3.8 g QD vs colesevelam 3.8 g QD	DB, MC, PC, PG, RCT Men and women with primary hypercholesterolemia	N=86 4-8 weeks washout period and 6 weeks of treatment	Primary: Mean percent change in LDL-C, mean absolute and mean percent change in HDL-C, non–HDL-C, TC, apo AI and apo B, and median absolute and percent changes in TG and hsCRP from baseline to end of treatment Secondary: Safety and tolerability	Primary: After 6 weeks of treatment, ezetimibe plus colesevelam produced a mean percent decrease in LDL-C of 32.3% vs 21.4% with ezetimibe monotherapy (P<0.0001). Ezetimibe plus colesevelam was significantly more effective than ezetimibe alone at producing mean percent reductions in TC, non–HDL-C, apo B and increases in apo AI (P<0.005 for all). Neither treatment regimen resulted in significant changes in median TG levels compared with baseline (P=NS). Secondary: Both treatment groups were safe and generally well tolerated.
Ansquer et al.[50] (2009) Ezetimibe 10 mg and fenofibrate 145 mg once daily vs ezetimibe 10 mg once daily vs	RCT, DB, MC Patients 18 to 70 years of age with type IIb dyslipidemia (LDL-C ≥160 mg/dl, TG 150-405 mg/dl) and ≥2 features of the metabolic syndrome according to the NCEP-ATP III definition	N=60 12 weeks	Primary: Percentage change from baseline in TG and HDL-C Secondary: Percentage change in LDL-C, non-HDL-C, remnant-like particle cholesterol (RLP-C) and related parameters, change in glucose	Primary: Fenofibrate/ezetimibe and fenofibrate reduced TG by -38.3% (P=NS) and raised HDL-C to a similar extent (+11.5% and +7.9%, respectively; P=0.282). Secondary: Fenofibrate/ezetimibe reduced LDL-C by -36.2% compared to -22.4% with fenofibrate and -22.8% with ezetimibe (both, P<0.001). Fenofibrate/ezetimibe lowered non-HDL-C by -36.2% compared to fenofibrate (-24.8%) and ezetimibe (-20.9%). There was no significant difference between fenofibrate/ezetimibe and fenofibrate with regards to RLP-C (-36.2% vs -30.7%; P=NS). Ezetimibe

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fenofibrate 145 mg once daily			metabolism parameters, and high-sensitivity C-reactive protein (hsCRP)	was less effective than fenofibrate/ezetimibe (-17.3%; P<0.001). The effect of fenofibrate/ezetimibe on LDL particle size (+2.1%) was similar to that of fenofibrate (+1.9%). Fenofibrate/ezetimibe was more effective than monotherapy with fenofibrate or ezetimibe in reducing apo B (-33.3%). Fenofibrate/ezetimibe had the same effect as fenofibrate on apo AI (+7.9% vs +5.1%, respectively) and apo AII (+24.2% vs +21.2%, respectively). Fenofibrate/ezetimibe and fenofibrate reduced hsCRP to a similar degree. There was a higher incidence of treatment-related adverse events with fenofibrate/ezetimibe, which was primarily due to abnormal laboratory changes, including moderate increases in CK, liver enzymes, and blood creatinine.
Farnier et al.[29] (2005) Ezetimibe 10 mg and fenofibrate 160 mg QD vs ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs placebo	DB, MC, PC, RCT Men and women 18 to 75 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%	N=619 12 weeks	Primary: Percent change in LDL-C from baseline to study end point Secondary: Percent change in other lipid, non-lipid, and lipoprotein parameters from baseline to study end point	Primary: The mean percent change in LDL-C reduction was significantly greater in the micronized fenofibrate and ezetimibe group when compared with the other treatment groups (P<0.001 compared with micronized fenofibrate and ezetimibe). These reductions were –13.4% in the ezetimibe group, –5.5% in the micronized fenofibrate group, and –20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared with micronized fenofibrate or ezetimibe monotherapy, significant reductions in apo B, non–HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; P<0.001. When compared with placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; P<0.001. The percent changes from baseline to study end point were as follows: –11.8% in TC, 3.9% in HDL-C, –11.1% in TG, and –6.1% in high sensitivity CRP in the ezetimibe group; –10.8% in TC, 18.8% in HDL-C, –43.2% in TG, and –28.0% in HsCRP in the micronized fenofibrate group; –22.4% in TC, 19.0% in HDL-C, –44.0% in TG, and –27.3% in high sensitivity CRP in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the micronized fenofibrate and ezetimibe group; P<0.05 for all.
Tribble et al.[48] (2008) Ezetimibe 10 mg and fenofibrate 160 mg QD (FENO + EZE) vs ezetimibe 10 mg QD (EZE) vs fenofibrate 160 mg QD (FENO) vs placebo	RCT, DB, MC, PC Patients 18-75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dl and TG 200 to 500 mg/dl) and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution profiles and particle size	Primary: The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall. All active treatments reduced IDL-C. Treatment with FENO significantly reduced LDL-C1, LDL-C3, and LDL-C4 and significantly increased LDL-C2 compared to placebo. FENO + EZE produced a pattern of changes similar to those of FENO alone;. The reductions in LDL-C1 and LDL-C3 were greater with the combination due to the added effects of EZE. There were no significant changes in cholesterol associated with Lp(a). Fenofibrate and FENO + EZE increased median HDL-C2 and HDL-C3 compared with EZE and placebo. In patients treated with EZE, there were reductions in VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or changes in the HDL-C range. In patients treated with FENO, there were reductions in VLDL-C and IDL-C. HDL-C was increased and there was a shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall. In patients treated with FENO + EZE, there were reductions in VLDL-C, IDL-C, and LDL-C. HDL-C was increased and there was a shift from smaller, more dense to larger, more buoyant LDL subfractions. EZE did not significantly affect LDL peak particle size. FENO and FENO + EZE increased LDL peak particle size.
McKenney et al.[30] (2006) Ezetimibe 10 mg and fenofibrate	DB, ES, RCT Patients with mixed hyperlipidemia, LDL-C 130 to 220 mg/dL,	N=576 48 weeks	Primary: Percent change in LDL-C from baseline	Primary: The combination resulted in significantly reduced LDL-C compared with monotherapy (–22.0 vs –8.6; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
160 mg QD vs fenofibrate 160 mg QD	TG 200 to 500 mg/dL		Secondary: Percent change in TC, HDL-C, TG, non–HDL-C, apo B, apo AI, and HsCRP from baseline	The combination resulted in significantly reduced TC, TG, non–HDL-C, and apo B compared with monotherapy (–23.2 vs –13.6; P<0.001), (–46.0 vs –41.8; P=0.002), (–31.6 vs –19.4; P<0.001), (–25.2 vs –16.2; P<0.001). The combination resulted in significantly increased HDL-C compared with monotherapy (20.9 vs 17.8; P=0.02). There were no significant differences in apo AI or HsCRP (P=not significant).
Jelesoff et al.[39] (2006) Ezetimibe 10 mg daily and niacin vs niacin	RETRO Patients who received ezetimibe as add-on therapy to stable doses of niacin and other lipid medications	N=53 Not reported	Primary: TC, LDL-C, TG, HDL-C Secondary: Percent change in patients meeting NCEP ATP III treatment guidelines	Primary: The addition of ezetimibe resulted in reductions of 18%, 25%, and 17% (P<0.001) for TC, LDL-C, and TG, respectively. There were no significant differences in HDL-C (P=NS). Secondary: 13% of patients met goals prior to addition of ezetimibe while 45% of patients met goals following addition of ezetimibe (P<0.001).
Blagden et al.[32] (2007) Ezetimibe 10 mg and atorvastatin 10 mg QD vs atorvastatin 10 mg QD	DB, MC, PC, RCT Men and women with primary hypercholesterolemia and CHD	N=148 6 weeks	Primary: Mean percentage change in LDL-C from baseline to study end point Secondary: Percentage of patients achieving the new Joint British Society 2 (JBS 2) recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L, percentage of patients reaching	Primary: From baseline to week 6, ezetimibe and atorvastatin provided significantly greater reductions in adjusted mean LDL-C level compared with atorvastatin monotherapy, (–50.5% vs –36.5%; P<0.0001), equating to an additional 14.1% reduction (95% CI, –17.90 to –10.19). Secondary: A significantly higher proportion of patients on ezetimibe and atorvastatin achieved the new JBS 2 recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L compared with atorvastatin monotherapy (62% vs 12%; P<0.0001 and 93% vs 79%, respectively). Patients receiving ezetimibe and atorvastatin were 12 times more likely to reach LDL-C targets (OR, 12.1; 95% CI, 5.8 to 25.1; P<0.0001) compared with patients receiving atorvastatin monotherapy. Clinical chemistry profiles and the incidence of adverse events were similar in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			LDL-C targets, safety and tolerability	
Stein et al.[33] (2004) Ezetimibe 10 mg and atorvastatin 10 mg QD (titrated up to 40 mg/day) vs atorvastatin 20 mg QD (titrated up to 80 mg/day)	DB, DD, MC Patients ≥18 years of age with primary hypercholesterolemia and documented CHD, at least 2 cardiovascular risk factors, or heterozygous familial hypercholesterolemia with an LDL-C level ≥130 mg/dL despite treatment with atorvastatin 10 mg	N=621 14 weeks	Primary: Percentage of patients in the 2 treatment groups achieving an LDL-C level ≤100 mg/dL after 14 weeks randomization Secondary: Effects on other lipid parameters 4 weeks after randomization	Primary: When compared to atorvastatin monotherapy, a significantly higher percentage of patients in the ezetimibe and atorvastatin reached an LDL-C level ≤100 mg/dL after 14 weeks randomization, respectively 7% vs 22%; P<0.01. Secondary: When compared to atorvastatin monotherapy, significant reductions in LDL-C, TC and TG levels were observed in patients in the ezetimibe and atorvastatin; P<0.01. Respectively, percent changes between combination vs atorvastatin monotherapy were –22.8 vs –8.6% (mean change) in LDL-C levels, –17.3% vs –6.1% in TC levels (mean change), and –9.3% vs –3.9% (median change) in TG levels; P<0.01 for all. Nonsignificant changes were observed in HDL-C levels.
Zieve et al.[11] (2010) ZETELD Ezetimibe 10 mg for 12 weeks and atorvastatin 10 mg QD for 6 weeks, followed by atorvastatin 20 mg for 6 weeks vs atorvastatin 20 mg QD for 6 weeks, followed by atorvastatin 40 mg	RCT, DB, MC, PG Patients ≥65 years of age at high risk for coronary heart disease with or without atherosclerotic vascular disease (AVD) who had not reached a LDL-C <70 mg/dl or <100 mg/dl, respectively, after receiving atorvastatin 10 mg/day	N=1.053 12 weeks	Primary: Percent change in LDL-C after 6 weeks Secondary: Percentage of patients achieving LDL-C <70 mg/dl and <100 mg/dl for high-risk patients without AVD and <70 mg/dl for high-risk patients with AVD, HDL-C, non-HDL-C, TG, TG, apo B, apo A-I, TC:HDL-	Primary: After 6 weeks of therapy, treatment with ezetimibe + atorvastatin led to a significantly greater reduction in LDL-C compared to atorvastatin monotherapy (-29% vs -15%; P<0.001). Secondary: The percentage of patients achieving LDL-C <70 mg/dl and LDL-C <100 mg/dl (without AVD) or <70 mg/dl (with AVD) was significantly greater with ezetimibe + atorvastatin compared to atorvastatin monotherapy at week 6 and week 12 (P<0.001). After 6 weeks of therapy, treatment with ezetimibe + atorvastatin led to significantly greater changes in HDL-C (+3% vs +1%; P=0.02), TC (-16% vs -8%; P<0.001), non-HDL-C (-24% vs -11%; P<0.001), TG (-13% vs -6%; P<0.001), apo B (-17% vs -8%; P<0.001), TC:HDL-C (-17% vs -8%; P<0.001), LDL-C:HDL-C (-27% vs -13%; P<0.001), apo B:apo A-I (-15% vs -5%; P<0.001), and non- HDL-C:HDL-C (-24% vs -11%; P<0.001). At week 12, significantly greater changes in favor of ezetimibe +

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 6 weeks			C, apo B:apo A-I, LDL-C:HDL-C, non-HDL-C:HDL-C	atorvastatin occurred in HDL-C, TC, non-HDL-C, apo B, apo A-I, TC:HDL-C, LDL-C:HDL-C, apo B:apo A-I, and non-HDL-C:HDL-C. There was no significant difference among the treatment groups in apo A-I at week 6, high-sensitivity C-reactive protein at weeks 6 and 12, and TG at week 12.
Conard et al.[51] (2008) Ezetimibe 10 mg and atorvastatin 20 mg QD vs atorvastatin 40 mg QD	RCT, DB, MC, PG Patients 18 to 79 years of age at moderately high risk for coronary heart disease who were receiving atorvastatin 20 mg QD with LDL-C levels of 100 mg/dl to 160 mg/dl and TG ≤350 mg/dl	N=196 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <100 mg/dl, percent change TG, TC, HDL-C, non-HDL-C, apo A-I, apo B, TC: HDL-C, LDL-C:HDL-C, apo B:apo A-I, non-HDL-C:HDL-C, high sensitivity C-reactive protein	Primary: Treatment with ezetimibe/atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-31% vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe/atorvastatin achieved the NCEP ATP III LDL-C goal <100 mg/dl than with atorvastatin 40 mg (84% vs 49%, P<0.001). Treatment with ezetimibe/atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo A-I, and non-HDL-C:HDL-C than treatment with atorvastatin 40 mg (P<0.001). There was no significant difference in HDL-C, TG, apo A-I, and high-sensitivity C-reactive protein among the treatment groups.
Leiter et al.[52] (2008) Ezetimibe 10 mg and atorvastatin 40 mg QD vs atorvastatin 80 mg QD	RCT, DB, MC, PG Patients 18 to 79 years of age at high risk for coronary heart disease (CHD or those with a CHD risk equivalent medical condition) who were receiving atorvastatin 40 mg QD with LDL-C levels of 70 mg/dl to 160 mg/dl and TG ≤350 mg/dl	N=579 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <70 mg/dl, percent change TG, TC, HDL-C, non-HDL-C, apo A-I, apo B, TC: HDL-C, LDL-	Primary: Treatment with ezetimibe/atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-27% vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe/atorvastatin achieved the NCEP ATP III LDL-C goal <70 mg/dl than with atorvastatin 80 mg (74% vs 32%, respectively; P<0.001). Treatment with ezetimibe/atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo A-I, and non-HDL-C:HDL-C than treatment with atorvastatin 80 mg (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			C:HDL-C, apo B:apo A-I, non-HDL-C:HDL-C, high sensitivity C-reactive protein	There was no significant difference in HDL-C, TG, apo A-I, and high-sensitivity C-reactive protein among the treatment groups.
Ballantyne et al.[26] (2003) Ezetimibe 10 mg QD and atorvastatin 10 to 80 mg QD vs ezetimibe 10 mg QD vs atorvastatin 10 to 80 mg QD vs placebo	DB, PC, RCT Men and women aged ≥18 years with primary hypercholesterolemia (LDL-C 145-250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction in direct LDL-C from baseline to final assessment Secondary: Change from baseline to final assessment for calculated LDL-C, TC, TG, HDL-C, TC:HDL-C ratio, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a), direct LDL-C:HDL-C ratio, adverse events	Primary: There was a significantly greater mean reduction of direct LDL-C from baseline to final assessment in the ezetimibe plus atorvastatin group compared to either atorvastatin alone (P<0.01) or ezetimibe alone (P<0.01). Mean changes in direct LDL-C ranged from –50% to –60% in the combination group compared to –35% to –51% in the atorvastatin alone group (P<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly in the combination group than all doses of atorvastatin monotherapy (P<0.01). Greater reductions in LDL-C, TC, and TG were observed with increasing doses of atorvastatin monotherapy. However, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50% vs 51%), TC:HDL-C ratio (43% vs 41%), and TG (both 31%) with coadministration of ezetimibe plus atorvastatin 10 mg and the maximal dose of atorvastatin monotherapy, respectively. However, there was a significantly greater increase in HDL-C (9% vs 3%) with the combination group. Reductions in apo B, non–HDL-C, and direct LDL-C:HDL-C ratio from baseline were significantly greater in the combination group compared to both atorvastatin monotherapy (P<0.01 for all) and ezetimibe monotherapy (P<0.01 for all). However, increases in HDL_2-C (P=0.53), HDL_3-C (P=0.06), apo AI (P=0.31), and Lp(a) (P=0.50) did not significantly differ between the combination therapy and atorvastatin monotherapy groups. There also was no significant difference between the combination therapy and ezetimibe monotherapy groups for increases in these same parameters: HDL_2-C (P=0.08), HDL_3-C (P=0.67), apo AI (P=0.80), and Lp(a) (P=0.92).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The combination of ezetimibe plus atorvastatin was well-tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin monotherapy and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity.
Kerzner et al.[27] (2003) Ezetimibe 10 mg QD and lovastatin 10 to 40 mg QD vs ezetimibe 10 mg QD vs lovastatin 10 to 40 mg QD vs placebo	DB, MC, PC, RCT Men and women aged ≥18 years with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation, mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease in directly measured LDL-C from baseline to study end point Secondary: Change from baseline to end point for calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, direct LDL-C:HDL-C ratio, adverse events	Primary: The reduction in plasma levels of direct LDL-C from baseline to end point was significantly greater in the combination group of ezetimibe plus lovastatin compared to either lovastatin or ezetimibe monotherapy (P<0.01 for both). The mean percentage decrease in direct LDL-C in the combination group was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin monotherapy (P<0.01). The mean percentage change in LDL-C achieved with combination ezetimibe plus lovastatin 10 mg was similar to the highest lovastatin dose of 40 mg monotherapy (P=0.10). Secondary: In comparison to lovastatin monotherapy, the combination group significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, direct LDL-C:HDL-C ratio (P<0.01 for all), and apo AI (P=0.04). The combination of ezetimibe plus lovastatin significantly increased HDL-C at lovastatin doses of 20 and 40 mg compared to the same lovastatin monotherapy dose (P<0.01 and P<0.02, respectively) and significantly decreased TG levels (P<0.01 for both). Treatment-related adverse events were reported for 16% of patients receiving lovastatin monotherapy and 17% of patients receiving combination therapy. The safety profile for the combination group was similar to that for the lovastatin monotherapy and placebo group.
Melani et al.[28] (2003)	DB, MC, PC, RCT Men and women 20-86	N=538 12 weeks	Primary: Percent change in direct LDL-C from	Primary: A mean percent change of –38% for the combination therapy and –24% for pravastatin monotherapy was observed. The combination therapy was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD and pravastatin 10 to 40 mg QD vs ezetimibe 10 mg QD vs pravastatin 10 to 40 mg QD vs placebo	years old with primary hypercholesterolemia (LDL-C 150 to 250 mg/dl and TG ≤350 mg/dl)		baseline to study end point Secondary: Mean change and percent change from baseline in LDL-C as calculated by the Friedewald equation, TC, TG, HDL-C, direct LDL-C:HDL-C and TC:HDL-C ratio, non–HDL-C, apo AI, apo B, HDL_2-C, HDL_3-C, Lp(a)	significantly more effective at reducing plasma levels of direct LDL-C from baseline to end point (P<0.01). The combination group had a mean percentage change in direct LDL-C ranging from –34% to –41% compared with –20% to –29% for individual doses of pravastatin monotherapy. When the combination therapy was compared to its corresponding pravastatin dose, the incremental mean percentage reductions in direct LDL-C were statistically significant in favor of the combination therapy (P≤0.01). In addition, the coadministration of ezetimibe plus pravastatin 10 mg produced a larger mean percentage reduction in direct LDL-C compared to the highest dose of pravastatin monotherapy (P≤0.05). Secondary: In comparison to pravastatin monotherapy, the combination therapy improved calculated LDL-C, TG, TC, apo B, non–HDL-C, direct LDL-C:HDL-C, and TC:HDL-C (P<0.01 for all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced in the combination group (P<0.01). TG was also significantly reduced in the combination group at pravastatin doses of 10 and 20 mg compared to pravastatin monotherapy (P<0.05). Although the combination therapy produced greater increases in HDL-C at the 10 and 40 mg doses, it was not significant. The differences in change in HDL_2-C, HDL_3-C, apo AI, and Lp(a) between the combination group and pravastatin monotherapy were determined to be not significant (P=NS). Coadministration of ezetimibe and pravastatin was well tolerated and the overall safety profile was similar to pravastatin monotherapy and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any non-laboratory adverse event.
Strony et al.[46] (2008) Ezetimibe 10 mg coadministered	OL, MC, ES (Pooled analysis) Patients with primary hypercholesterolemia	N=795 (2 trials) 12 to 15 months	Primary: Tolerability Secondary: LDL-C, HDL-C,	Primary: Treatment-emergent adverse events (AEs) were reported in 81% of patients receiving ezetimibe + pravastatin (15 months) and in 84% of patients receiving ezetimibe + simvastatin (12 months).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with either pravastatin 10-40 mg or simvastatin 10-80 mg once daily			TG, TC, and proportion of patients achieving LDL-C goal	The most commonly reported treatment-emergent AEs were upper respiratory tract infection (18%), headache (11%), musculoskeletal pain (10%), arthralgia (10%), sinusitis (10%), abdominal pain (8%), bronchitis (6%), coughing (6%), nausea (6%), back pain (5%), myalgia (5%), chest pain (5%), and fatigue (5%) with ezetimibe + pravastatin. The most commonly reported treatment-emergent AEs were upper respiratory tract infection (19%), arthralgia (11 %), musculoskeletal pain (10%), headache (9%), back pain (8%), myalgia (8%), abdominal pain (7%), nausea (7%), pharyngitis (6%), coughing (5%), fatigue (5%), and urinary tract infection (19%). During the ezetimibe + pravastatin extension study, 7% experienced serious adverse events (SAEs). During the ezetimibe + simvastatin extension study, SAEs were reported in 10% of patients. Life-threatening AEs were reported in 4 patients in the ezetimibe + simvastatin study. The incidence of newly reported AEs did not increase over time in either study. In the ezetimibe + pravastatin study, 1% of patients experienced increases in ALT/AST >3 X ULN, whereas this was not reported in the patients receiving ezetimibe + simvastatin. Secondary: The mean LDL-C was reduced by 36.5% and 40.4% in the ezetimibe + pravastatin and ezetimibe + simvastatin studies, respectively. Similar reductions in TC and TG, and an increase in HDL-C, were achieved and maintained throughout the study period in both studies. In the ezetimibe + pravastatin study, 85% of patients achieved their NCEP ATP III LDL-C goal and 80% of patients in the ezetimibe + simvastatin study achieved their recommended goal.
Ballantyne et al.[34] (2007) Ezetimibe 10 mg	MC, OL, PG, RCT Men and women aged ≥18 years with	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III	Primary: Significantly more patients in the combination therapy group achieved the LDL-C goal of <100 mg/dL at week 6 compared to rosuvastatin alone (94% vs 79.1%; P<0.001).

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and rosuvastatin 40 mg QD vs rosuvastatin 40 mg QD	hypercholesterolemia, history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent (10-year CHD risk score >20%), 2 most recent fasting LDL-C levels of ≥160 mg/dL and <250 mg/dL		LDL-C goal (<100 mg/dL) after 6 weeks of treatment Secondary: Percentage of patients achieving the ATP III non–HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL, percentage of patients achieving the 2003 European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals of <100 or 115 mg/dL and <175 or 190 mg/dL, respectively, depending on risk category, percentage change from baseline in LDL, HDL, TC, TG, non-HDL, lipid ratios (LDL:HDL, TC:HDL and non-HDL:HDL), apo AI, apo B, and apo B:apo AI ratio, and	Secondary: The non–HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL were achieved by a significantly higher percentage of patients in the combination therapy group than the monotherapy group (88 patients or 37.4% and 80 patients or 34.8%, respectively; P<0.001). There was a significantly higher percent of patients in the combination therapy group achieving the European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals (LDL <100 or 115 mg/dL and TC <175 or 190 mg/dL), depending on risk category compared to the rosuvastatin group alone at week 6 (LDL 93.6% vs 74.3%, LDL and TC 90.6% vs 68.3%, respectively; P<0.001). At week 6, the combination therapy group had a significantly greater percent reduction of 69.8% in the LDL level compared to a 57.1% reduction in the monotherapy group (P<0.001). Significantly greater reductions in TC, non–HDL-C and TG levels were seen in the combination group compared to the monotherapy group (P<0.001). Both treatment groups increased HDL level to a similar extent (P=0.151). LDL:HDL, TC:HDL and non-HDL:HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared to patients receiving monotherapy (all P<0.001). Significant decreases in apo B and the apo B:apo AI ratio were seen in the combination therapy group compared to the monotherapy group (P<0.001 for both). Apo AI increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively (P=0.202). The median percent decrease in CRP was significantly higher with combination therapy than monotherapy (–46.4% vs –28.6%; P<0.001). The overall frequency and type of adverse events were similar in both groups, with 31.5% of patients on combination therapy and 33.5% of patients on monotherapy reporting any adverse event. No adverse events were considered related to ezetimibe; the most frequently reported adverse event was myalgia (3.0% of patients in the rosuvastatin-alone group and 2.9% in the rosuvastatin plus ezetimibe group). There were 2 patients

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			changes in HsCRP in at week 6, safety and tolerability	(0.8%) in the combination therapy group and 3 patients (1.3%) in the monotherapy group who discontinued the study due to treatment-related adverse events. One death occurred in the combination therapy group due to acute myocardial infarction and this was not considered to be related to study treatment. ALT increases >3 times the upper limit of normal were recorded in 3 patients, all in the combination therapy group.
Patel et al.[35] (2006) Ezetimibe 10 mg and simvastatin 20 mg QD vs simvastatin 20 mg QD	DB, MC, PC, PG, RCT Men and women aged 18-75 years with primary hypercholesterolemia (LDL ≥3.3 mmol/L and ≤4.9 mmol/L, TG <3.99 mmol/L) and documented CHD at least 3 months prior to baseline who were not receiving pharmacologic lipid management therapy	N=153 6 weeks	Primary: Mean change in LDL cholesterol level from baseline to 6 weeks and the proportion of patients who reached an LDL goal of <3 mmol/L at end point Secondary: Changes in serum TC, TG and HDL levels, and safety and tolerability	Primary: At 6 weeks, patients receiving ezetimibe and simvastatin combination therapy had a mean LDL reduction of 14.6% (95% CI, 10.1 to 19.1). At 6 weeks, a greater number of patients receiving ezetimibe and simvastatin combination therapy reached an LDL goal <3 mmol/L compared to patients receiving monotherapy (93% vs 75%; P<0.001). Secondary: At 6 weeks, there was a significant additional reduction in TC of 0.69 mmol/L in patients receiving ezetimibe and simvastatin combination therapy compared to patients receiving ezetimibe monotherapy (95% CI, 0.48 to 0.90; P<0.0001). There was a 20.4% reduction in TG levels in the combination group compared to a 12.4% reduction in the monotherapy group (P=0.06). Baseline HDL levels increased by 6% in both treatment groups. In the combination group, 40% of patients had at least one treatment-emergent adverse event compared to 25% in the monotherapy group. The overall incidence of adverse events were not significant among the two groups (P=0.07). Two patients in the combination therapy group and 1 patient in the monotherapy group experienced a serious adverse event unrelated to the study medications.
Landry et al.[36] (2006) Ezetimibe 10 mg and simvastatin 20 mg QD	MC, RCT Men and women ≥18 years of age, patients on pre-dialysis with creatinine level ≥1.7 mg/dL, hemodialysis,	N=203 6 months	Primary: LDL-C, TC, non–HDL-C, HDL-C, TG, apo B, apo AI Secondary: Tolerability and	Primary: Both groups had statistically reduced LDL-C at 1, 3, and 6 months compared to baseline (P<0.0001). The addition of ezetimibe to simvastatin was associated with 27%, 26%, and 21% reductions in LDL-C at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 16%, 16%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 20 mg QD	or peritoneal dialysis		safety	and 14% reductions in TC at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 24%, 25%, and 19% reductions in non–HDL-C at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 15%, 14%, and 12% reductions in apo B at 1, 3, and 6 months, respectively. There were no significant effects in HDL-C, TG, or apo AI (P=not significant) except for 7% increase of HDL-C at 3 months (P=0.02). Secondary: There were no significant differences in muscle pain, muscle weakness, abdominal discomfort, nausea, constipation, or appetite loss between groups (P=NS). More patients on ezetimibe reported diarrhea (27% vs 12%; P=0.009). There were no significant differences in CK levels or abnormal hepatic transaminase levels.
Bays et al.[45] (2008) Ezetimibe 10 mg and simvastatin 10 to 80 mg QD vs simvastatin 20 to 80 mg QD	RCT, DB, MC, ES Patients ≥18 years of age with primary hypercholesterolemia (LDL-C 145 to 250 mg/dl and TG ≤350 mg/dl)	N=768 48 weeks	Primary: Safety and tolerability Secondary: Percent change in LDL-C, TC, HDL-C, TG, apo B, apo A-I, apo A-II, apo E, Lp(a), LDL-C:HDL-C ratio, high sensitivity C-reactive protein (hsCRP), fibrinogen and proportion of patients achieving NCEP ATP II	Primary: Treatment with ezetimibe/simvastatin and simvastatin monotherapy did not differ with regards to total AEs (73% vs 69%), treatment-related AEs (13.5% vs 11.4%), treatment-related SAEs (1% vs 0%), discontinuations due to treatment-related AEs (2.8% vs 2.6%), discontinuations due to SAEs (1.1% vs 0.4%), or discontinuations due to treatment-related SAEs (1 vs 0%). Treatment with ezetimibe/simvastatin and simvastatin monotherapy did not differ with regards to total laboratory AEs (12% vs 12%), treatment-related laboratory AEs (6.2% vs 5.3%), total laboratory SAEs (0% vs 0%), treatment-related laboratory SAEs (0% vs 0%), or discontinuations due to laboratory SAEs (0% vs 0%). Changes in ALT and AST were dose-related in both treatment groups. The pooled incidence of enzyme levels greater than 3 times the ULN for each treatment are 3.0% and 0.9% (P>0.10) for ALT and 2.1% and 0.4% (P>0.10) for AST for ezetimibe/simvastatin and simvastatin monotherapy,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			LDL-C goals	respectively. The pooled incidence of CK levels 5 to 10 times the ULN were 0.2% and 0.0% (P>0.99) for ezetimibe/simvastatin and simvastatin monotherapy, respectively. No cases of myopathy were observed in either group. Secondary: Treatment with ezetimibe/simvastatin led to greater reductions in LDL-C than simvastatin monotherapy (51% vs 40%, respectively; P<0.001), TC (36% vs 28%, respectively; P<0.001), and TG (25% vs 18%, respectively; P<0.001). There was no difference in HDL-C among the treatment groups. There was no significant difference among the treatment groups in apo A-I, apo A-II, apo E, Lp(a), and fibrinogen (P>0.05). Treatment with ezetimibe/simvastatin led to significantly greater changes in hsCRP compared to simvastatin monotherapy (P<0.001). The percentage of patients achieving LDL-C cholesterol goals with ezetimibe/simvastatin and simvastatin monotherapy were as follows: LDL-C <130 mg/dl (90% vs 85%, respectively), LDL-C <100 mg/dl (76% vs 46%, respectively), and LDL-C <70 mg/dl (34% vs 4.8%, respectively).
van der Graaf et al.[49] (2008) <u>Step 1</u> Ezetimibe 10 mg and simvastatin 10 to 40 mg once daily for 6 weeks vs simvastatin 10 to 40 mg once daily for 6 weeks	RCT, DB, MC, PC Patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH)	N=248 53 weeks	Primary: Percent change from baseline in LDL-C after 6 weeks Secondary: TC, HDL-C, TG, non-HDL-C, apo B after 6 weeks, 33 weeks and 53 weeks, percentage of patients achieving LDL-C goals	Primary: After 6 weeks of therapy, ezetimibe + simvastatin lowered LDL-C by -49.5% compared to -34.4% with simvastatin monotherapy (P<0.01). Secondary: After 6 weeks of therapy, ezetimibe + simvastatin was more effective than simvastatin monotherapy in lowering TC (-38.2% vs 26.3%; P<0.01), non-HDL-C (-46.8% vs -32.7%; P<0.01), and apo B (-38.9% vs -26.7%; P<0.01). There was no significant difference in HDL-C (P<0.95) or TG (P<0.48) among the treatment groups. After 33 weeks of therapy, ezetimibe + simvastatin was more effective than simvastatin monotherapy in lowering LDL-C (-54% vs 38.1%; P<0.01), TC (-42.5% vs 29.3%; P<0.01), non-HDL-C (-51.3% vs -35.7%; P<0.01), TG (-20% vs -13.4%; P<0.01) and apo B (-42.6% vs -27.9%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Step 2 Ezetimibe 10 mg and simvastatin 40 mg once daily for 27 weeks vs simvastatin 40 mg once daily for 27 weeks Step 3 Ezetimibe 10 mg and simvastatin 10 to 40 mg once daily for 20 weeks				P<0.01). There was no significant difference in HDL-C (P=0.58) among the treatment groups. The percentage of patients achieving the American Academy of Pediatrics acceptable LDL-C goal of <130 mg/dl and ideal LDL-C goal of <110 mg/dl was significantly higher with ezetimibe + simvastatin 40 mg (77% and 63%, respectively) compared to simvastatin 40 mg monotherapy (53% and 27%, respectively; P<0.01). After 53 weeks of therapy, the mean percent change in LDL-C in the overall population was -49.1% from baseline. Mean percent changes were -38.5% in TC, -46.4% in non–HDL-C, and median percent changes of -16.6% were observed in TG. The HDL-C levels were 3.3% above baseline levels at the end of step 3.
Gagné et al.[18] (2002) Ezetimibe 10 mg QD and statin therapy vs statin monotherapy	DB, MC, PC, RCT Adults aged ≥18 years, currently on a stable daily dose of a statin for ≥6 weeks, must have been previously instructed on a cholesterol-lowering diet, LDL-C at or above recommended target level for patient's risk category (<160 mg/dL for patients without CHD and ≤1 risk factor, <130 mg/dL for patients without CHD and ≥2 risk factors,	N=769 8 weeks	Primary: Mean percentage change in LDL-C from baseline to end point Secondary: Percentage of patients who achieved NCEP ATP II target levels for LDL-C, HDL-C, TC, TG, adverse events	Primary: There was an additional LDL-C reduction of 25.1% in patients receiving ezetimibe therapy compared to a reduction of 3.7% in patients receiving placebo (P<0.001 for between-group differences). Secondary: Including patients who were technically at LDL-C goal at baseline, 75.5% of patients taking ezetimibe plus statin achieved the prespecified NCEP ATP II target LDL-C levels at end point compared to 27.3% of patients taking placebo plus statin (OR, 19.6; P<0.001). For those patients who were not at target LDL-C levels at baseline, 71.5% vs 18.9% of patients taking ezetimibe and placebo, respectively, achieved target LDL-C goals. HDL-C was increased by 2.7% compared with an increase of 1.0% in patients taking ezetimibe and placebo, respectively (P<0.05). TG decreased by 14.0% and 2.9%, respectively (P<0.001). TC was also improved significantly with coadministration of ezetimibe compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≤100 mg/dL for patients with established but stable CHD or CHD-equivalent disease)			placebo (P<0.001). The overall incidence of treatment-related adverse events was similar between both groups (21% ezetimibe vs 17% placebo).
Denke et al.[21] (2006) Ezetimibe 10 mg QD and statin therapy vs statin monotherapy	DB, MC, PC, PG, RCT Men and women ≥18 years of age with diabetes, metabolic syndrome without diabetes, or neither disorder who had LDL levels exceeding the NCEP ATP III goals who were taking a stable, approved dose of any statin, had been following a cholesterol –lowering diet for at least 6 weeks prior to study entry with TG levels ≤350 mg/dL	N=3,030 6 weeks	Primary: LDL reduction and additional lipid parameters, safety and tolerability	Primary: After 6 weeks of treatment, the addition of ezetimibe to ongoing statin therapy reduced LDL levels in patients with diabetes by 28%, metabolic syndrome by 24%, or elevated LDL levels without diabetes or the metabolic syndrome by 26%, compared with a 3% reduction in the placebo group (P<0.001 for all). TG and HDL levels were significantly reduced in patients with diabetes and metabolic syndrome when ezetimibe was added to statin therapy compared to placebo (P<0.002). Non-HDL levels, TC, apo B:apo A-I ratio, and CRP levels improved significantly in patients with diabetes and patients with elevated LDL levels without diabetes or metabolic syndrome when ezetimibe was added to statin therapy compared to placebo. Drug-related adverse events occurred in 5.2% in the placebo group and 5.1% in the ezetimibe group. Drug-related adverse events that led to drug discontinuation occurred in 1.6% in the placebo group and 0.9% in the ezetimibe group. There were no significant differences between the two groups in elevation of ALT, AST or in muscle CK beyond predefined limits.
Pearson et al.[23] (2006) Ezetimibe 10 mg QD and statin therapy vs statin monotherapy	DB, MC, PG, PC, RCT Men and women ≥18 years of age including white, African American, Hispanic or other who followed a cholesterol-lowering diet, were taking a stable approved dose of any US-marketed statin for at least 6	N=3,030 6 weeks	Primary: LDL-C and additional parameters and percentage of patients reaching LDL goal for the NCEP ATP III in racial and ethnic subgroups Secondary:	Primary: The addition of ezetimibe to ongoing statin therapy significantly reduced LDL, TC, non-HDL and HDL levels compared to placebo (P<0.001). This effect was consistent across race and ethnicity (P>0.50 for treatment-by-race interactions). CRP level reduction was statistically significant in patients receiving ezetimibe compared to placebo (P<0.001). The treatment-by-race interaction was not statistically significant (P=0.83), indicating a consistent treatment effect of lowering CRP levels across race and ethnicity groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	weeks before study entry, with LDL levels greater than the NCEP ATP III goal		Safety and tolerability	Ezetimibe added to statin therapy significantly increased the percentage of patients attaining their LDL-C goal for the NCEP ATP III in African Americans by 63%, Hispanics by 64.8% and whites by 72.3%, compared to placebo (P<0.001). Secondary: The addition of ezetimibe to ongoing statin therapy was well tolerated with an overall safety profile similar in all patient groups by race or ethnicity.
Simons et al.[24] (2007) Ezetimibe 10 mg QD and statin therapy vs statin monotherapy	OL Men and women from Australia, mean age 65.6 years, with CHD or diabetes mellitus who had already used ≥40 mg/day of a statin for at least 3 months with current TC of >4 mmol/L for existing CHD or >6.5 mmol/L for diabetes or >5.5 mmol/L for diabetes if HDL is <1.0 mmol/L	N=130 6 weeks	Primary: LDL reduction and percentage of patients who reached LDL goal of <2.5 mmol/L or <2.0 mmol/L and other lipid parameters	Primary: The LDL levels after 6 weeks were reduced by 29% (95% CI, 25 to 34) in patients receiving ezetimibe. Goal LDL-C of <2.5 mmol/L and <2.0 mmol/L were reached in 70% and 50% of patients receiving ezetimibe (95% CI, 59% to 79% and 39% to 60%, respectively). TC and TG levels were reduced by 19% and 11%, respectively, in the ezetimibe group compared to placebo (95% CI, –21 to –16 and –16 to –5). There were no significant changes in HDL between the two groups (95% CI, 0 to 6).
Mikhailidis et al.[25] (2007) Ezetimibe 10 mg QD and statin therapy vs statin monotherapy	MA Adults ≥18 years with diagnoses of nonfamilial or familial hypercholesterolemia, hyperlipidemia, and homozygous familial sitosterolemia; with LDL-C levels above NCEP ATP II/III guideline criteria	N=5,039 (21 trials) 6 to 48 weeks	Primary: Total number of patients attaining LDL-C goal; changes in TC, LDL-C, and HDL-C from baseline to end point	Primary: The analysis of 5 RCTs indicated that when compared to placebo in combination with a statin, the RR of obtaining the LDL-C treatment goal was higher for patients in the ezetimibe and statin groups; P<0.0001. A weighted mean difference (WMD) between treatments significantly favored the ezetimibe and statin combination therapy over placebo and statin: for TC, a WMD of –16.1% (CI, –17.3 to –14.8); for LDL-C, a WMD of –23.6% (CI, –25.6 to –21.7); and for HDL-C, a WMD of 1.7% (CI, 0.9 to 2.5); P<0.0001 for all. In an analysis of patients with or without CHD (in addition to hypercholesterolemia), the ezetimibe and statin combination was favored

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				over placebo and statin for the following WMD: LDL-C –23.6% (P<0.0001); TC –16.1% (P<0.0001); HDL-C +1.7% (P<0.0001); TG –10.7%; Apo B –17.3%; RR, LDL-C treatment goal 3.4 (P<0.0001). The difference between treatments in all studies favored the ezetimibe and statin combination therapy for all outcomes except TG and HDL-C. An analysis of data from a 48-week extension study correlated with the pooled estimates of the short-term studies in the meta-analysis. This data showed that the ezetimibe and simvastatin combination resulted in significantly lower levels of LDL-C, TC, and TG when compared with the placebo and simvastatin combination (reductions of 20.4%, 13.4% and 13.6%, respectively; P<0.001 for the difference between treatments).
Pearson et al.[53] (2009) Group 1 Ezetimibe 10 mg QD vs placebo Group 1 Ezetimibe 10 mg QD added to baseline statin therapy vs placebo added to baseline statin therapy	MA Patients with hypercholesterolemia and high-sensitivity C-reactive protein ≤10 mg/L	N=5,271 (11 trials) 6-12 weeks	Primary: Mean change in high-sensitivity C-reactive protein (CRP) and LDL-C	Primary: Treatment with ezetimibe monotherapy led to a mean 1% reduction in CRP compared to a mean 5% increase with placebo after 12 weeks (P=0.09). Treatment with ezetimibe/statin combination therapy led to a mean 12% decrease in CRP compared to a mean 1% decrease with statin monotherapy after 6 to 8 weeks (P<0.001). Treatment with ezetimibe monotherapy led to a mean 18% reduction in LDL-C compared to a mean 0.5% increase with placebo after 12 weeks of therapy (P<0.001). Treatment with ezetimibe/statin combination therapy led to a mean 27% decrease in LDL-C compared to a mean 3% decrease with statin monotherapy after 6 to 8 weeks (P<0.001).
Bissonnette et al.[20] (2006)	MC, OL, PRO Men and women ≥18	N=953 6 weeks	Primary: Percentage of change in LDL-C	Primary: After 6 weeks of treatment with ezetimibe, a statistically significant mean reduction was observed in LDL-C (30.5%; P<0.001).

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Ezetimibe 10 mg QD and statin therapy	years of age with a confirmed diagnoses of hypercholesterolemia and elevated plasma LDL-C levels of ≥2.5 mmol/L for patients at high 10-year CAD risk, ≥3.5 mmol/L for patients at moderate 10-year CAD risk and ≥4.5 mmol/L for patients at low 10-year CAD risk category, on a stable diet and statin regimen for at least 4 weeks before study entry		during the 6-week treatment period Secondary: Percentage of patients who had achieved the recommended target LDL-C levels at the end of the 6-week treatment period and the percentage of change in TC, TG, HDL-C, apo B and the TC:HDL-C ratio and safety and tolerability	Secondary: At 6 weeks, 674 patients (80.5%) achieved the recommended target LDL-C levels. After 6 weeks of treatment with ezetimibe, statistically significant mean reductions were observed in TC (20.8%), TG (10.1%), apo B (19.8%), and TC:HDL ratio (19.9%) (P<0.001). There were 50 mild, nonserious adverse events related to ezetimibe reported by 32 patients (3.4%). Frequently reported adverse events included constipation (0.7%), diarrhea (0.4%) and dizziness (0.4%).
Pitsavos et al.[44] (2009) Ezetimibe 10 mg QD added to high-dose statin therapy	OL Patients with heterozygous familial hypercholesterolemia who were receiving treatment with high-dose statins (atorvastatin 80 mg, pravastatin 40 mg, rosuvastatin 40 mg, simvastatin 80 mg, fluvastatin 80 mg)	N=70 12 months	Primary: Lipid and lipoprotein parameters	Primary: After 3 months, treatment with ezetimibe + statin led to a significant reduction in TC (P<0.05), LDL-C (P<0.05), TG (P<0.05) and apo-B (P<0.05), which persisted until 12 months. There were no significant changes in HDL-C, apo-A, Lp(a), fibrinogen or hsCRP with ezetimibe + statin.
Trials Assessing Atherosclerosis Progression and Cardiovascular Outcomes				
Kastelein et al.[37] (2008) ENHANCE	DB, MC, PRO, RCT Men and women between the ages of 30	N=720 24 months	Primary Change in mean carotid artery IMT (defined as average	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (P=0.29).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg and simvastatin 80 mg once daily vs simvastatin 80 mg daily	and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without treatment; patients were excluded if they had high-grade stenosis or occlusion of the carotid artery, history of carotid endarterectomy or carotid stenting, homozygous FH, NYHA class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris or recent cardiovascular events		of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; P=0.92) or new plaque formation (2.8% vs 4.7%; P=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; P=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (P=0.93), carotid bulb (P=0.37), internal carotid artery (P=0.21) and femoral artery (P=0.16) or average of the mean values for carotid and femoral artery IMT (P=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-group difference of 16.5%; P<0.01). Reductions in TG (between-group difference of 6.6%; P<0.01) and CRP (between-group difference of 25.7%; P<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone. Adverse events (29.5% vs 34.2%; P=0.18) and discontinuation rates (9.4% vs 8.1%; P=0.56) were similar between simvastatin monotherapy and the combination therapy.
Rossebø et al.[43] (2008) SEAS Ezetimibe 10 mg and simvastatin 40 mg once daily	RCT, MC, DB Patients 45-85 years of age who had asymptomatic, mild-to-moderate aortic valve stenosis with a peak aortic-jet velocity of 2.5 to 4 m per second	N=1,873 Median 52.2 months	Primary: Composite of major cardiovascular events (death from cardiovascular causes, aortic-valve replacement,	Primary: The composite of major cardiovascular events occurred in 35.3% of patients in the simvastatin/ezetimibe group and in 38.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.83 to 1.12; P=0.59). Secondary: There was no significant difference between the treatments in aortic-valve–related events (HR, 0.97; 95% CI, 0.83 to 1.14; P=0.73).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Open-label lipid-lowering therapy could be administered in addition to the study drug.			congestive heart failure as a result of progression of aortic-valve stenosis, nonfatal myocardial infarction, hospitalization for unstable angina, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or non-hemorrhagic stroke) Secondary: Aortic-valve events, progression of aortic stenosis, safety	Aortic-valve replacement occurred in 28.3% of patients in the simvastatin/ezetimibe group and in 29.9% of patients in the placebo group (HR, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Ischemic cardiovascular events occurred in 15.7% of patients in the simvastatin/ezetimibe group compared to 20.1% of patients in the placebo group (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.02). A total of 7.3% of patients in the simvastatin-ezetimibe group required CABG compared to 10.8% of patients in the placebo group (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.02). There was no significant difference in the progression of aortic stenosis between the treatment groups. The mean peak aortic jet velocity was 3.71 m per second in the placebo group compared to 3.69 m per second in the simvastatin/ezetimibe group at the end of the study (95% CI, −0.06 to 0.05; P=0.83). The mean pressure gradient increased to 34.4 mm Hg in the placebo group compared to 34.0±15.1 mm Hg in the simvastatin/ezetimibe group at the end of the study. There was no significant difference in the aortic-valve area between the treatment groups. There was no significant difference in overall mortality among the treatment groups (P=0.80). The composite outcome of death from cardiovascular causes and the individual components of this composite outcome did not differ significantly between the two groups (P=0.34). There was a significant increase in the number of patients with elevated liver enzyme levels in the simvastatin/ezetimibe group. There was also a higher incidence of cancer in the simvastatin/ezetimibe group (11.1%) compared to placebo (7.5%; P=0.01).
Fleg et al.[47] (2008) SANDS	RCT, OL (Subgroup analysis) American Indian men and women ≥40 years	N=427 3 years	Primary: Change in carotid intima-media thickness (CIMT) after 36 months of	Primary: After 36 months, CIMT progressed in the standard group and regressed in the aggressive subgroups (ezetimibe + statin and statin monotherapy; P<0.001 vs the standard group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD and statin therapy (aggressive treatment arm) vs statin monotherapy (aggressive treatment arm) Patients in the standard treatment arm served as the control group for this post-hoc analysis.	of age with type 2 diabetes, LDL-C >100 mg/dl, systolic blood pressure >130 mm Hg, and no prior CV events This trial examined the effects of aggressive goals for LDL-C (<70 mg/dl), non–HDL-C (<100 mg/dl), and blood pressure (<115/75 mm Hg) reduction vs standard goals of <100 mg/dl, <130 mg/dl, and <130/80 mm Hg, respectively.		treatment	There was a similar percent of patients in the aggressive treatment arms who demonstrated no change or a decrease in CIMT with ezetimibe + statin compared to statin monotherapy (62% vs 61%, respectively). Only 39% of patients in the standard arm demonstrated no change or a decrease in CIMT (P<0.0001 vs the aggressive arm). Cardiovascular events occurred in 3.5%, 5.8%, and 3.3% of patients in the standard, aggressive with ezetimibe + statin, and aggressive statin monotherapy subgroups, respectively (P=0.62).
Taylor et al.[42] (2009) Ezetimibe 10 mg once daily vs niacin SR (Niaspan®) 2 g (titrated) once daily	RCT, OL, PG Patients ≥30 years of age with atherosclerotic coronary or vascular disease or a coronary heart disease risk equivalent (diabetes mellitus, 10-year Framingham risk score ≥20%, coronary calcium score >200 for women or >400 for men who were receiving treatment with a statin (LDL-C <100 mg/dl and HDL-	N=208 14 months	Primary: Change in carotid intima-media thickness (IMT) after 14 months Secondary: Change in lipid values, composite of major adverse cardiovascular events (myocardial infarction, myocardial revascularization, admission to the hospital for an acute coronary	Primary: Treatment with niacin led to a significant reduction in mean and maximal carotid intima–media thickness at 8 months (P=0.001 and P=0.004, respectively) and 14 months (P=0.001 and P<0.001, respectively). There was no significant change in mean or maximal carotid intima–media thickness with ezetimibe at 8 or 14 months compared to baseline. There was a significant difference between the niacin group and the ezetimibe group (P=0.003). Secondary: The change in LDL-C in the ezetimibe group was −17.6 mg/dl compared to -10.0 mg/dl in the niacin group (P=0.01). The change in HDL-C in the ezetimibe group was −2.8 mg/dl compared to 7.5 mg/dl in the niacin group (P<0.001). There were significant reductions in triglycerides in both groups. Major adverse cardiovascular events occurred in 5% of patients receiving ezetimibe compared to 1% of patients receiving niacin (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	C <50 mg/dl for men or <55 mg/dl for women)		syndrome, and death from coronary heart disease), discontinuation of study drug due to adverse effects, and health-related quality of life	Adverse drug effects led to withdrawal from the study in 3 of 9 patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12). There was no significant difference between the two groups in the quality of life at baseline or at 14 months.

Drug regimen abbreviations: QD=daily
Study abbreviations: CI=confidence interval, DB=double=blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, RR=relative risk, SB=single blind, SD=standard deviation, WMD=weighted mean difference, XO=cross over
Miscellaneous abbreviations: apo AI=apolipoprotein AI, apo B=apolipoprotein B, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CK=creatine kinase, CRP=C-reactive protein, FH=familial hypercholesterolemia, HAART=highly active antiretroviral therapy, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, HDL_2=HDL subfraction 2, HDL_3=HDL subfraction 3, HIV=human immunodeficiency virus, hsCRP=high-sensitivity C-reactive protein, IMT=intima-media thickness, JBS=Joint British Society, LDL-C=low-density lipoprotein cholesterol, LDL-C:HDL-C=low-density lipoprotein cholesterol:high-density lipoprotein cholesterol ratio, Lp(a)=lipoprotein(a), NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, non–HDL-C=non-high-density lipoprotein cholesterol, NYHA=New York Heart Association, TC=total cholesterol, TC:HDL-C=total cholesterol:high-density lipoprotein cholesterol ratio, TG=triglyceride, VLDL=very low-density lipoprotein

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Cholesterol Absorption Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ezetimibe	tablet	Zetia®	$$$$	N/A

N/A=Not available

X. Conclusions

Ezetimibe is the only cholesterol absorption inhibitor in this class and it is not available in a generic formulation. It is approved for the treatment of primary hypercholesterolemia, mixed hyperlipidemia, homozygous familial hypercholesterolemia and homozygous familial sitosterolemia.[4]

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes (TLC).[5-10] For patients who cannot achieve LDL-C goals with the use of a statin alone, the addition of another LDL-C lowering drug such as niacin, a bile acid sequestrant or ezetimibe is recommended.[5,7-10]

Clinical trials have demonstrated that monotherapy with ezetimibe significantly lowers total cholesterol, LDL-C, apolipoprotein B and triglycerides, as well as increases HDL-C compared to placebo.[4,12-17,22] Complementary effects on various lipid/lipoprotein parameters were also observed in clinical trials when ezetimibe was

coadministered with colesevelam, fenofibrate, niacin and statins.[11,18,21,23-30,32-33,38-39,45,48-52] The effects of ezetimibe given either alone or in addition to a statin or fenofibrate on cardiovascular morbidity and mortality have not been established.[4] Ezetimibe should be available as adjunctive therapy through the medical justification portion of the prior authorization process.

Therefore, all brand cholesterol absorption inhibitors 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 cholesterol absorption 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 Fibric Acid Derivatives
AHFS Class 240606
August 11, 2010

I. Overview

The antilipemic agents are categorized into 5 different AHFS classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their FDA-approved indications, mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apo CIII.[4-11] The resulting decrease in triglycerides produces an alteration in the size and composition of LDL cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of HDL cholesterol (HDL-C), as well as apo AI and AII.[4-11] The fibric acid derivatives can decrease triglycerides by 20% to 50% and increase HDL-C by 10% to 35%.[13] They also lower LDL-C by 5% to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.

There are several fenofibrate products that are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose.[3] Fenofibric acid is the active metabolite of fenofibrate.

The fibric acid derivatives that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Fenofibrate (micronized and non-micronized formulations), fenofibric acid and gemfibrozil are available in a generic formulation. This class was last reviewed in May 2008.

Table 1. Fibric Acid Derivatives Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fenofibrate	capsule, tablet	Fenoglide®, Lipofen®, Lofibra®*	fenofibrate
Fenofibrate, micronized	capsule	Antara®, Lofibra®*	fenofibrate, micronized
Fenofibrate, nanocrystallized	tablet	Tricor®, Triglide®	none
Fenofibric acid	delayed-release capsule, tablet	Fibricor®*, Trilipix®	fenofibric acid
Gemfibrozil	tablet	Lopid®*	gemfibrozil

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the fibric acid derivatives are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Fibric Acid Derivatives

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart	General Recommendations • Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • Fibrates may have an adjunctive role in the treatment of patients with

Clinical Guideline	Recommendation(s)
Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[12]** **(2004)**	high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high-risk patients with high TG or low high-density lipoprotein (HDL) levels as the predominant lipoprotein abnormality, consideration can be given to combination therapy with fibrates or nicotinic acid and a low-density lipoprotein cholesterol (LDL-C)-lowering agent. • When an LDL-C-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • If a high-risk person has high TG or low HDL-C levels, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When TG are >200 mg/dL, non–HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal. <u>Familial Defective Apolipoprotein B-100 (FDB)</u> • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. <u>Polygenic Hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report[13]** **(2002)**	<u>General Recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. • If triglycerides are very high (≥500 mg/dL), triglyceride-lowering drugs (fibrate or nicotinic acid) become first line therapy.

Clinical Guideline	Recommendation(s)
	Fibric Acid Derivatives (Fibrates) • Fibrates can be recommended for persons with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-very low density lipoproteins). • Fibrate therapy should be considered for those with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in persons who have elevated LDL-C and atherogenic dyslipidemia.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies**[14] **(2007)**	• Statins are considered first-line drugs for lowering LDL cholesterol. • Fibric acid derivatives are considered useful only for the treatment of patients with low HDL, high TG, and other characteristics of insulin resistance syndrome and type 2 diabetes. • Fibrate monotherapy cannot be recommended as first-line therapy in diabetic patients but may be considered in those with persistently low HDL levels or severely elevated TG. • When TG are between ~450-900 mg/dL, fibrates (or statins) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update**[15] **(2006)**	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy.
Institute for Clinical Systems Improvement (ICSI): **Lipid Management in Adults**[16] **(2009)**	• For monotherapy, statins are the drugs of choice for lowering LDL. • If patients are unable to take statins, then bile-acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile-acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
National Institute for Health and Clinical Excellence (NICE): **Lipid Modification**[17] **(2008)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a ≥20% 10-year risk of developing CVD. • Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered for the primary prevention of CVD. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary

Clinical Guideline	Recommendation(s)
	prevention of CVD. • Statin therapy is recommended for adults with clinical evidence of CVD. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dl) or LDL-C <2 mmol/L (<77 mg/dl) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association[46] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
American Heart Association (AHA)/American Stroke Association (ASA): **Primary Prevention of Ischemic Stroke[47] (2006)**	• Patients with known CAD and high-risk hypertensive patients (even with normal LDL cholesterol levels) should be treated with lifestyle measures and a statin. • For patients with low HDL-C, consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL. • For patients with elevated Lp[a], consider niacin in conjunction with glycemic control and LDL-C control.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the fibric acid derivatives 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 Fibric Acid Derivatives[1-12]

Indication	Fenofibrate	Fenofibric Acid	Gemfibrozil
Hypertriglyceridemia			
Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia)	✔		
Adjunctive therapy to diet for treatment of severe hypertriglyceridemia		✔	

Indication	Fenofibrate	Fenofibric Acid	Gemfibrozil
Adjunctive therapy to diet for the treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet			✔ †
Primary Hypercholesterolemia and Mixed Dyslipidemia			
Adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, triglycerides, and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia	✔	✔	
Adjunctive therapy to diet in combination with a statin to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal		✔ ‡	
Adjunctive therapy to diet to reduce the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol) and who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides			✔

†Patients who present such risk typically have serum triglycerides over 2,000 mg/dl and have elevations of very low-density lipoprotein cholesterol (VLDL)-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Patients who consistently have total serum or plasma TG below 1,000 mg/dL are unlikely to present a risk of pancreatitis. Gemfibrozil may be considered for those patients with triglyceride elevations between 1000 and 2000 mg/dl who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis.
‡Trilipix®

IV. Pharmacokinetics

The pharmacokinetic parameters of the fibric acid derivatives are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Fibric Acid Derivatives[1-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fenofibrate	60-90	99	Liver, Kidneys	Renal (60-93) Feces (5-25)	20-22
Fenofibric acid	81	99	Conjugation with glucuronic acid	Renal	20
Gemfibrozil	Well absorbed	99	Liver, extensive	Renal (70) Feces (6)	1.5

V. Drug Interactions

Significant drug interactions with the fibric acid derivatives are listed in Table 5.

Table 5. Significant Drug Interactions with the Fibric Acid Derivatives[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Fibric acid derivatives (fenofibrate, fenofibric acid, gemfibrozil)	1	Anticoagulants	Fibric acid derivatives may potentiate the inhibition of vitamin K dependent clotting factor synthesis by anticoagulants. The hypoprothrombinemic effect of anticoagulants may be increased by fibric acid derivatives and bleeding may occur.
Fenofibrate	1	Statins	Severe myopathy may occur if fenofibrate and statins are coadministered. If coadministration of these agents cannot be avoided, closely monitor creatine kinase.
Gemfibrozil	1	Cerivastatin	Gemfibrozil appears to cause a significant increase in cerivastatin systemic exposure by a mechanism that has yet to be established. Plasma concentrations and pharmacologic effects of cerivastatin may be increased by gemfibrozil.
Gemfibrozil	1	Statins	Severe myopathy and rhabdomyolysis may occur if gemfibrozil and statins are coadministered. If coadministration of these agents cannot be avoided, closely monitor creatine kinase.
Gemfibrozil	2	Bexarotene	Inhibition of cytochrome P450 3A4-mediated metabolism of bexarotene may be inhibited by gemfibrozil. Plasma concentrations and pharmacologic effects of bexarotene may be increased by gemfibrozil.
Gemfibrozil	2	Meglitinides	Inhibition of cytochrome P450 2C8 by gemfibrozil may decrease the metabolic elimination of meglitinides. Plasma concentrations and pharmacologic effects of meglitinides may be increased by gemfibrozil. The risk of excessive hypoglycemia may be increased.
Gemfibrozil	2	Rosiglitazone	Gemfibrozil may increase the plasma concentrations and pharmacologic effects of rosiglitazone. The effect of gemfibrozil on plasma concentrations of rosiglitazone may be mediated by gemfibrozil-induced inhibition of cytochrome P450 2C8.
Gemfibrozil	2	Sulfonylureas	Gemfibrozil may increase or decrease plasma glucose concentrations in diabetic patients treated with sulfonylureas.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the fibric acid derivatives are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Fibric Acid Derivatives[1-12]

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Cardiovascular			
Angina pectoris	✔	-	-
Arrhythmia	✔	-	-
Atrial fibrillation	✔	-	1
Cardiovascular disorder	✔	-	-
Coronary artery disorder	✔	-	-
Edema	✔	-	-
Electrocardiogram abnormal	✔	-	-
Hypertension	✔	✔	-
Hypesthesia	-	-	✔
Hypotension	✔	-	-
Migraine	✔	-	-
Myocardial infarction	✔	-	-
Palpitation	✔	-	-
Peripheral edema	✔	-	-
Peripheral vascular disorder	✔	-	✔
Phlebitis	✔	-	-
Syncope	-	-	✔
Tachycardia	✔	-	-
Varicose vein	✔	-	-
Vascular disorder	✔	-	-
Vasodilatation	✔	-	-
Ventricular extrasystoles	✔	-	-
Central Nervous System			
Anxiety	✔	-	-
Confusion	-	-	✔
Convulsion	-	-	✔
Depression	✔	-	✔
Dizziness	✔	3-4	✔
Fatigue	-	2-3	4
Fever	✔	-	-
Headache	3	12-13	1
Hypertonia	✔	-	-
Insomnia	✔	✔	-
Libido decreased	✔	-	✔
Nervousness	✔	-	-
Neuralgia	✔	-	-
Paresthesia	✔	-	✔
Pain	✔	-	-
Peripheral neuritis	-	-	✔
Somnolence	✔	-	✔
Vertigo	✔	-	2
Dermatological			
Acne	✔	-	-
Alopecia	✔	-	-
Angioedema	-	-	✔
Contact dermatitis	✔	-	-
Eczema	✔	-	2

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Exfoliative dermatitis	-	-	✔
Fungal dermatitis	✔	-	-
Herpes simplex	✔	-	-
Herpes zoster	✔	-	-
Nail disorder	✔	-	-
Maculopapular rash	✔	-	-
Photosensitivity reaction	✔	-	✔
Pruritus	✔	-	-
Rash	-	-	2
Skin disorder	✔	-	-
Skin ulcer	✔	-	-
Stevens-Johnson syndrome	✔	✔	-
Sweating	✔	-	-
Toxic epidermal necrolysis	✔	✔	-
Urticaria	✔	-	✔
Vasculitis	-	-	✔
Endocrine and Metabolic			
Diabetes mellitus	✔	-	-
Gout	✔	-	-
Gynecomastia	✔	-	-
Hypoglycemia	✔	-	-
Hyperuricemia	✔	-	-
Gastrointestinal			
Abdominal pain	5	✔	10
Anorexia	✔	-	-
Cholestatic jaundice	-	-	✔
Colitis	✔	-	-
Constipation	2	3	1
Diarrhea	2	3-4	7
Duodenal ulcer	✔	3-5	-
Dyspepsia	✔	-	20
Eructation	✔	-	-
Esophagitis	✔	-	-
Flatulence	✔	-	-
Nausea	2	4-6	2
Peptic ulcer	✔	-	-
Vomiting	✔	-	2
Weight gain/loss	✔	-	-
Genitourinary			
Creatinine increased	✔	-	-
Cystitis	✔	-	-
Decreased male fertility	-	-	✔
Dysuria	✔	-	-
Impotence	-	-	✔
Kidney function abnormal	✔	-	✔
Nephrotoxicity	✔	✔	✔
Prostatic disorder	✔	-	-
Unintended pregnancy	✔	-	-
Urinary frequency	✔	-	-
Urinary tract infection	-	✔	-
Vaginal moniliasis	✔	-	-
Hematologic			
Agranulocytosis	✔	✔	-
Anemia	✔	✔	✔

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Ecchymosis	✔	-	-
Eosinophilia	✔	-	-
Hematocrit decreased	-	✔	-
Hemoglobin decreased	-	✔	-
Leukopenia	✔	✔	✔
Lymphadenopathy	✔	-	-
Thrombocytopenia	✔	✔	✔
Hepatic			
Alkaline phosphokinase increased	-	-	✔
ALT increased	3	1-3	✔
AST increased	3	✔	✔
Bilirubin increased	-	-	✔
Cirrhosis	✔	✔	-
CPK increased	3	✔	✔
Hepatic enzymes increased	✔	✔	-
Hepatitis	✔	✔	-
Jaundice	-	-	✔
Liver fatty deposit	✔	-	-
Laboratory Test Abnormalities			
Serum creatinine increased	✔	✔	-
Musculoskeletal			
Arthralgia	✔	4	✔
Arthritis	✔	-	-
Arthrosis	✔	-	-
Bursitis	✔	-	-
Back pain	3	4-6	-
Joint disorder	✔	-	-
Leg cramps	✔	-	-
Muscle pain/spasm	✔	3-4	-
Myalgia	✔	3-4	-
Myasthenia	✔	-	✔
Myopathy	✔	-	✔
Myositis	✔	✔	-
Painful extremities	-	3-5	✔
Paresthesia	✔	-	✔
Rhabdomyolysis	✔	✔	✔
Synovitis	-	-	✔
Tenosynovitis	✔	-	-
Weakness	✔	✔	-
Respiratory			
Asthma	✔	-	-
Bronchitis	✔	✔	-
Cough	✔	✔	-
Dyspnea	✔	-	-
Laryngeal edema	-	-	✔
Laryngitis	✔	-	-
Nasopharyngitis	-	4-5	-
Pharyngitis	✔	-	-
Pneumonia	✔	-	-
Pulmonary embolism	✔	✔	-
Respiratory disorder	6	-	-
Rhinitis	2	-	-
Sinusitis	✔	3-4	-
Upper respiratory infection	-	4-5	-

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Other			
Allergic reaction	✔	-	-
Amblyopia	✔	-	-
Anaphylaxis	-	-	✔
Appendicitis, acute	-	-	1
Asthenia	2	-	-
Blurred vision	-	-	✔
Cataracts	✔	-	✔
Chest pain	✔	-	-
Cholecystitis	✔	-	✔
Cholelithiasis	✔	✔	✔
Conjunctivitis	✔	-	-
Cyst	✔	-	-
Deep vein thrombosis	✔	✔	-
Drug-induced lupus syndrome	-	-	✔
Dry mouth	✔	-	-
Ear pain	✔	-	-
Eye disorder	✔	-	-
Flu syndrome	2	-	-
Hernia	✔	-	-
Hypersensitivity reaction	✔	✔	-
Infection	✔	-	-
Influenza	-	✔	-
Intracerebral hemorrhage	-	-	✔
Malaise	✔	-	-
Otitis media	✔	-	-
Pancreatitis	✔	✔	✔
Pharyngolaryngeal pain	-	✔	-
Raynaud's phenomenon	-	-	✔
Refraction disorder	✔	-	-
Retinal edema	-	-	✔
Seizure	-	-	✔
Syncope	-	-	✔
Taste perversion	-	-	✔
Vision abnormalities	✔	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the fibric acid derivatives are listed in Table 7.

Table 7. Usual Dosing Regimens for the Fibric Acid Derivatives[1-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Fenofibrate (Fenoglide®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 120 mg per day Hypertriglyceridemia: 40 to 120 mg per day	Safety and efficacy in pediatric patients have not been established.	Tablet: 50 mg 150 mg
Fenofibrate (Lipofen®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 150 mg per day	Safety and efficacy in pediatric patients have not been established.	Capsule: 50 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertriglyceridemia: 50 to 150 mg per day		
Fenofibrate (Lofibra®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 160 mg per day Hypertriglyceridemia: 54 to 160 mg per day	Safety and efficacy in pediatric patients have not been established.	Tablet: 54 mg 160 mg
Fenofibrate (Triglide®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 160 mg per day Hypertriglyceridemia: 50 to 160 mg per day	Safety and efficacy in pediatric patients have not been established.	Tablet: 50 mg 160 mg
Fenofibrate, micronized (Antara®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 130 mg per day Hypertriglyceridemia: 43 to 130 mg per day	Safety and efficacy in pediatric patients have not been established.	Capsule: 43 mg 130 mg
Fenofibrate, micronized (Lofibra®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 200 mg per day Hypertriglyceridemia: 67 to 200 mg per day	Safety and efficacy in pediatric patients have not been established.	Capsule: 67 mg 134 mg 200 mg
Fenofibrate, nanocrystallized (Tricor®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 145 mg per day Hypertriglyceridemia: 48 to 145 mg per day	Safety and efficacy in pediatric patients have not been established.	Tablet: 48 mg 145 mg
Fenofibric acid (Fibricor®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: 105 mg per day Severe Hypertriglyceridemia: 35 to 105 mg per day	Safety and efficacy in pediatric patients have not been established.	Tablet: 35 mg 105 mg
Fenofibric acid (Trilipix®)	Coadministration Therapy with Statins for the Treatment of Mixed Dyslipidemia: 135 mg per day Primary Hypercholesterolemia or Mixed Hyperlipidemia: 135 mg per day Severe Hypertriglyceridemia: 45 to 135 mg per day	Safety and efficacy in pediatric patients have not been established.	Capsule (DR): 45 mg 135 mg
Gemfibrozil (Lopid®)	Type IIb Dyslipidemia or Hypertriglyceridemia: 600 mg twice daily	Safety and efficacy in pediatric patients have not been established.	Tablet: 600 mg

DR=delayed-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the fibric acid derivatives are summarized in Table 8. Clinical trials have not been conducted with Lipofen®.[4] The pharmacological effects of fenofibric acid have been extensively studied through oral administration of fenofibrate, which is converted in vivo to fenofibric acid.[9]

Table 8. Comparative Clinical Trials with the Fibric Acid Derivatives

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Rosenson et al.[25] (2007) Fenofibrate 160 mg QD vs placebo	DB, PC, R Patients with fasting hypertriglyceridemia (≥1.7 and <6.9 mmol/L) and 2 or more of the NCEP ATP III criteria for the metabolic syndrome	N=59 19 weeks	Primary: Fasting TG, postprandial TG, oxidative stress, inflammatory response	Primary: Fenofibrate treatment lowered fasting TG (–46.1%; P<0.0001) and postprandial (area under the curve) TG (–45.4%; P<0.0001) due to significant reductions in postprandial levels of large (–40.8%; P<0.0001), medium (–49.5%; P<0.0001) and VLDL particles. The number of fasting total LDL particles was reduced in fenofibrate-treated patients (–19.0%; P=0.0033) primarily due to reductions in small LDL particles (–40.3%; P<0.0001); these treatment differences persisted postprandially. Fasting and postprandial oxidized fatty acids were reduced in fenofibrate-treated patients compared with placebo-administered patients (–15.3%; P=0.0013, and 31.0%; P<0.0001, respectively). Fenofibrate therapy lowered inflammatory markers as follows: fasting and postprandial soluble VCAM-1 decreased by –10.9% for fasting VCAM-1 (P=0.0005), and by –12.0% for postprandial VCAM-1 (P=0.0001); and fasting and postprandial soluble ICAM-1 decreased by –14.8% for fasting ICAM-1 (P<0.0001) and by –15.3% for postprandial ICAM-1 (P<0.0001). Reductions in VCAM-1 and ICAM-1 were correlated with reductions in fasting and postprandial large VLDL particles (P<0.0001) as well as postprandial oxidized fatty acids (P<0.0005).
Davidson et al.[26] (2006) TRIMS Fenofibrate 130 mg QD	DB, MC, PC, RCT Patients between the ages of 21 and 79 years, with fasting TG levels ≥300 and <1,000 mg/dL, and at	N=146 8 weeks	Primary: Changes or percent changes from baseline to the end-of-treatment in fasting TG	Primary: There was a significant change from baseline in the mean percent decrease of TG in the fenofibrate group (36.6%) compared with essentially no change in the placebo group (P<0.001). Secondary: There was no significant difference in TC change between the fenofibrate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	least two of four additional components of the metabolic syndrome as defined by the NCEP ATP III		Secondary: Changes or percent changes from baseline in TC, LDL-C, HDL-C, the TC:HDL-C ratio, VLDL-C, non–HDL-C; apo AI, B, and C-III; and remnant lipoprotein cholesterol	treatment and the placebo groups (P=0.085). LDL-C increased by a mean of 15.0% in the fenofibrate group compared with 3.2% in the placebo group (P=0.006). HDL-C increased by a mean of 14.0% in the fenofibrate group compared with 0.8% for placebo (P<0.001). The ratio of TC to HDL-C decreased with fenofibrate compared with placebo (–14.2% vs 0.8%; P<0.001). VLDL-C declined by 33% with fenofibrate compared with a 1.6% decline with placebo treatment (P<0.001). Non–HDL-C decreased significantly more in the fenofibrate group (–7.5% vs –1.1%; P=0.009). There was no significant difference in the rise in apo AI among the fenofibrate group vs the placebo response (5.3% vs 2.0%; P=0.212). Apo B declined significantly with fenofibrate compared with placebo (P<0.001, respectively). Apo CIII was markedly reduced in the fenofibrate group (P<0.001 compared with placebo). A significant reduction in remnant lipoprotein cholesterol was observed with fenofibrate treatment (–35.1% vs 12.3%; P<0.001).
Hogue et al.[40] (2008) Fenofibrate 200 mg once daily vs atorvastatin 20 mg once daily	RCT Patients with type 2 diabetes and hypertriglyceridemia	N=40 6 weeks	Primary: Lipids and triglyceride-rich lipoproteins (TRL), inflammation and adhesion molecules	Primary: Treatment with atorvastatin led to a significant decrease in plasma TC (-37.7%; P<0.0001), plasma TG (-37.6%, P<0.0001), plasma apo B (-43.2%, P<.0001), TRL-C (-44.1%, P<0.0001), TRL-TG (-36.9%, P<0.0001), TRL apo B (-13.8%, P=0.04), LDL-C (-43.0%, P<0.0001), LDL apo B (-42.7%, P<0.0001), and a significant increase in HDL-C (+17.9%, P=0.001), and HDL apo A-I levels (+10.3%, P=0.004). Treatment with fenofibrate led to a significant decrease in plasma C (-10.9%, P=0.0001), plasma TG (-41.4%, P=0.0002), plasma apo B

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(-9.9%, P=0.01), TRL-C (-52.8%, P<0.0001), TRL-TG (-46.3%, P=0.0002), and TRL apo B (-14.8%, P=0.02) and a significant increase in LDL-C (+15.9%, P=0.04) and HDL-C (+8.9%, P=0.05). There were significant differences in the percentage changes of plasma C, plasma apo B, LDL-C, and LDL apo B between the 2 treatment groups. There was no significant difference in the percentage in changes of plasma TG between the treatment groups. Treatment with atorvastatin significantly decreased plasma levels of CRP (-26.9%, P=0.004), sICAM-1 (-5.4%, P=0.03), sVCAM-1 (-4.4%, P=0.008), sE-selectin (-5.7%, P=0.02), MMP-9 (-39.6%, P=0.04), sPLA2 (-14.8%, P=0.04), and oxLDL (-38.4%, P<0.0001). Fenofibrate significantly decreased sE-selectin levels only (-6.0, P=0.04) and increased sPLA2 levels (+22.5%, P=0.004).
Alrasadi et al.[39] (2008) <u>Protocol 1</u> Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g twice daily for 8 weeks <u>Protocol 2</u>	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC/HDL-C ratio	Primary: <u>Protocol 1</u> The mean percent change in HDL-C was +6%, -6%, and +22% in patients receiving fenofibrate, atorvastatin and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19%, -26% and -22% in patients receiving fenofibrate, atorvastatin and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). <u>Protocol 2</u> The mean percent change in HDL-C was -2% and +18% in patients receiving fenofibrate + atorvastatin and niacin + atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +32% and -32% in patients receiving fenofibrate + atorvastatin and niacin + atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC/HDL-C (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g twice daily and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2				
Koh et al.[27] (2006) Fenofibrate 200 mg QD and candesartan 16 mg QD vs fenofibrate 200 mg QD vs candesartan 16 mg	DB, PC, R, XO Patients with hypertriglyceridemia (≥150 mg/dL) and hypertension (≥140/90 mm Hg)	N=46 6 months	Primary: Blood pressure, lipid profile, inflammatory markers, vasomotor function, plasma malondialdehyde, adiponectin, and insulin resistance	Primary: Fenofibrate, combined therapy, or candesartan therapy significantly reduced blood pressure. However, combined therapy significantly reduced blood pressure more than fenofibrate or candesartan alone (P<0.001). When compared with candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile. Fenofibrate alone or combined therapy significantly lowered TC, TG, apo B, and non–HDL-C levels (all P<0.001) and increased HDL-C levels (P<0.001) when compared with baseline. These reductions were significantly greater than those observed with candesartan alone (P<0.001). However, there were no significant differences between fenofibrate alone and fenofibrate plus candesartan for these parameters (P=NS). All three treatment arms significantly improved flow-mediated dilator

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD				response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde (a biomarker for oxidative stress), HsCRP, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared with monotherapy (P<0.001, P=0.002, P=0.050, and P=0.032, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, the magnitudes of these increases were not significantly different among the three therapies (P=0.246 for adiponectin levels and P=0.153 for insulin sensitivity).
Ansquer et al.[41] (2009) Fenofibrate (Tricor®) 145 mg and ezetimibe 10 mg once daily vs fenofibrate (Tricor®) 145 mg once daily vs ezetimibe 10 mg once daily	RCT, DB, MC Patients 18 to 70 years of age with type IIb dyslipidemia (LDL-C ≥160 mg/dl, TG 150-405 mg/dl) and ≥2 features of the metabolic syndrome according to the NCEP-ATP III definition	N=60 12 weeks	Primary: Percentage change from baseline in TG and HDL-C Secondary: Percentage change in LDL-C, non-HDL-C, remnant-like particle cholesterol (RLP-C) and related parameters, change in glucose metabolism parameters, and high-sensitivity C-reactive protein (hsCRP)	Primary: Fenofibrate/ezetimibe and fenofibrate reduced TG by -38.3% (P=NS) and raised HDL-C to a similar extent (+11.5% and +7.9%, respectively; P=0.282). Secondary: Fenofibrate/ezetimibe reduced LDL-C by -36.2% compared to -22.4% with fenofibrate and -22.8% with ezetimibe (both, P<0.001). Fenofibrate/ezetimibe lowered non-HDL-C by -36.2% compared to fenofibrate (-24.8%) and ezetimibe (-20.9%). There was no significant difference between fenofibrate/ezetimibe and fenofibrate with regards to RLP-C (-36.2% vs -30.7%; P=NS). Ezetimibe was less effective than fenofibrate/ezetimibe (-17.3%; P<0.001). The effect of fenofibrate/ezetimibe on LDL particle size (+2.1%) was similar to that of fenofibrate (+1.9%). Fenofibrate/ezetimibe was more effective than monotherapy with fenofibrate or ezetimibe in reducing apo B (-33.3%). Fenofibrate/ezetimibe had the same effect as fenofibrate on apo AI (+7.9% vs +5.1%, respectively) and apo AII (+24.2% vs +21.2%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fenofibrate/ezetimibe and fenofibrate reduced hsCRP to a similar degree. There was a higher incidence of treatment-related adverse events with fenofibrate/ezetimibe, which was primarily due to abnormal laboratory changes, including moderate increases in CK, liver enzymes, and blood creatinine.
Farnier et al.[28] (2005) Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD vs placebo	RCT, DB, MC, PC Patients 18-75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dl and TG 200 to 500 mg/dl) and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Percent change in LDL-C from baseline to study end point after treatment with fenofibrate plus ezetimibe vs fenofibrate alone Secondary: Percent change from baseline to study end point in TC, TG, non–HDL-C, HDL-C, apo B, apo AI	Primary: There was a significantly greater percent reduction in LDL-C among patients in the fenofibrate plus ezetimibe group vs the fenofibrate only group (P>0.001). Secondary: Non–HDL-C and apo B were significantly reduced with fenofibrate plus ezetimibe when compared with fenofibrate or ezetimibe alone (P>0.001). TG levels were significantly decreased and HDL-C was significantly increased with fenofibrate plus ezetimibe when compared with placebo (P<0.001).
Tribble et al.[44] (2008) Fenofibrate 160 mg QD and ezetimibe 10 mg QD (FENO + EZE)	RCT, DB, MC, PC Patients 18-75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dl and TG 200 to 500 mg/dl) and no CHD or CHD-risk	N=625 12 weeks	Primary: Changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution	Primary: The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall. All active treatments reduced IDL-C. Treatment with FENO significantly reduced LDL-C1, LDL-C3, and LDL-C4 and significantly increased LDL-C2 compared to placebo. FENO + EZE produced a pattern of changes similar to those of FENO alone;. The reductions in LDL-C1 and LDL-C3 were greater with the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fenofibrate 160 mg QD (FENO) vs ezetimibe 10 mg QD (EZE) vs placebo	equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria		profiles and particle size	combination due to the added effects of EZE. There were no significant changes in cholesterol associated with Lp(a). Fenofibrate and FENO + EZE increased median HDL-C2 and HDL-C3 compared with EZE and placebo. In patients treated with EZE, there were reductions in VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or changes in the HDL-C range. In patients treated with FENO, there were reductions in VLDL-C and IDL-C. HDL-C was increased and there was a shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall. In patients treated with FENO + EZE, there were reductions in VLDL-C, IDL-C, and LDL-C. HDL-C was increased and there was a shift from small, dense to larger, more buoyant LDL subfractions. EZE did not significantly affect LDL peak particle size. FENO and FENO + EZE increased LDL peak particle size.
McKenney et al.[30] (2006) Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non–HDL-C, apo B, apo AI,	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared with fenofibrate alone (–22.0 vs –8.6; P<0.001). Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (–23.2 vs –13.6; P<0.001), TG (–46.0 vs –41.0; P=0.002), non–HDL-C (–31.6 vs –19.4; P<0.001), and apo B (–25.2 vs –16.2; P<0.001) compared with fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; P=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; P=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe 10 mg QD for 12 weeks, then fenofibrate 160 mg and ezetimibe 10 mg QD for 48 weeks vs placebo for 12 weeks, then fenofibrate 160 mg for 48 weeks			and HsCRP	Reductions in median HsCRP levels were not different between treatments (–25.3 vs –21.1; P=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.
Farnier et al.[29] (2007) Fenofibrate 160 mg and simvastatin-ezetimibe 20/10 mg once daily vs fenofibrate 160 mg once daily vs simvastatin-ezetimibe 20/10 mg once daily vs placebo	DB, MC, PA, PC, R Patients 18 to 79 years old with mixed hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change in LDL-C from baseline to study end point Secondary: Percent change from baseline to study end point in TC, TG, non–HDL-C, HDL-C, apo AI, and apo B	Primary: LDL-C level was significantly reduced with simvastatin-ezetimibe plus fenofibrate (–45.8%) compared with fenofibrate (–15.7%) or placebo (–3.5%; P<0.01), but not when compared with simvastatin-ezetimibe (–47.1%; P>0.2). Secondary: HDL-C and apo AI levels were significantly increased with simvastatin-ezetimibe plus fenofibrate (18.7% and 11.1%; P<0.01, respectively) treatment compared with simvastatin-ezetimibe (9.3% and 6.6%; P<0.01) or placebo (1.1% and 1.6%; P<0.01), but not when compared with fenofibrate (18.2% and 10.8%; P>0.2). TG, non–HDL-C, and apo B levels were significantly reduced with simvastatin-ezetimibe plus fenofibrate (–50.0%, –50.5%, and –44.7%; P<0.01, respectively) vs all other treatments.
Farnier et al.[42]	RCT, DB, MC, PC	N=611	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Fenofibrate 160 mg and ezetimibe-simvastatin 10/20 mg once daily vs fenofibrate 160 mg once daily vs ezetimibe-simvastatin 10/20 mg once daily vs placebo	Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or CHD risk score >20% (as defined by NCEP ATP III), LDL-C 130 to 220 mg/dl and TG 150 to 500 mg/dl	12 weeks	Percent change in cholesterol associated with lipoprotein subfractions (VLDL-C 1+2 and VLDL-C 3, IDL-C, LDL-C 1 to 4, Lp[a], HDL-C_2 and HDL-C_3, and changes in LDL particle size)	The effects of ezetimibe/simvastatin, fenofibrate, and ezetimibe/simvastatin + fenofibrate on VLDL subclasses were similar to those for VLDL-C overall. The maximal changes in IDL-C are achieved by ezetimibe/simvastatin with little additional effect of fenofibrate. Significant reductions were observed for all LDL-C subfractions with ezetimibe/simvastatin treatment. When coadministered with fenofibrate, the effects of both treatments were evident. Ezetimibe/simvastatin + fenofibrate resulted in a pattern of changes that were similar to fenofibrate monotherapy indicating that the change in LDL-C pattern was primarily a function of fenofibrate. There was no significant difference in cholesterol associated with Lp[a] among the treatment groups. Fenofibrate and ezetimibe/simvastatin + fenofibrate led to similar increases in median HDL-C_2 and HDL-C_3 compared to ezetimibe/simvastatin and placebo. Ezetimibe/simvastatin did not significantly affect LDL particle size. Fenofibrate and ezetimibe/simvastatin + fenofibrate increased LDL particle size. At the end of the study, the percentages of patients exhibiting LDL size pattern B was 64%, 49%, 14%, and 17% in the placebo, ezetimibe/simvastatin, fenofibrate, and ezetimibe/simvastatin + fenofibrate groups, respectively.
Derosa et al.[45] (2009) Fenofibrate 145 mg/day and simvastatin 40 mg/day vs	RCT, DB, MC Caucasian patients ≥18 years of age with type 2 diabetes mellitus and combined dyslipidemia who had never been treated with lipid-	N=241 12 months	Primary: Lipid and lipoprotein profiles at 6 and 12 months	Primary: After 6 months of therapy, there was a significant reduction in TC and LDL-C with simvastatin and fenofibrate + simvastatin (P<0.05 and P<0.01, respectively). There was no significant change in the fenofibrate group. After 12 months of therapy, there was a significant decrease in TC and LDL-C in all treatment groups (P<0.05 for fenofibrate, P<0.01 for the simvastatin and P<0.001 for fenofibrate + simvastatin). TC was significantly lower with fenofibrate + simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). LDL-C was significantly lower with fenofibrate + simvastatin compared to simvastatin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fenofibrate 145 mg/day vs simvastatin 40 mg/day	lowering medications			monotherapy and fenofibrate monotherapy (P<0.01). After 6 months of therapy, there was a significant reduction in TG with fenofibrate and fenofibrate + simvastatin (P<0.05, respectively). There was no significant change in the simvastatin group. After 12 months of therapy, there was a significant decrease in TG in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate + simvastatin). TG was significantly lower with fenofibrate + simvastatin compared to fenofibrate (P<0.05)or simvastatin (P<0.01). After 6 months of therapy, there was a significant increase in HDL-C with fenofibrate and fenofibrate + simvastatin (P<0.05 and P<0.01, respectively). There was no change in the simvastatin group. After 12 months of therapy, there was a significant increase in HDL-C in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate + simvastatin). HDL-C was significantly higher with fenofibrate + simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). After 6 months of therapy, there was no significant change in Apo A-1 or Apo B in any treatment group. After 12 months of therapy, there was a significant increase of Apo A-1 with fenofibrate + simvastatin. There was no significant difference between the treatment groups. After 12 months of therapy, there was a significant decrease of Apo B in all groups (P<0.05 for fenofibrate, P<0.05 for simvastatin and P<0.01 for fenofibrate + simvastatin). There was no significant difference between the treatment groups. There were no significant differences in Lp(a) after 6 or 12 months of therapy in any of the treatment groups. After 6 months of therapy, there was a significant decrease in hs-CRP with fenofibrate + simvastatin (P<0.05), but not in the other groups. After 12 months of therapy, there was a significant decrease in hs-CRP with simvastatin and with fenofibrate + simvastatin (P<0.05 and P<0.01, respectively), but not with fenofibrate. The hs-CRP value was significantly lower with fenofibrate + simvastatin compared to fenofibrate or simvastatin (P<0.05).
May et al.[38]	RCT, DB, SC, PC	N=300	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) DIACOR Fenofibrate 160 mg and simvastatin 20 mg once daily vs fenofibrate 160 mg once daily vs simvastatin 20 mg once daily	Patients with type 2 diabetes, no CHD, and biochemical evidence of mixed dyslipidemia (having 2 of the following 3 lipid parameters: LDL-C >100 mg/dl, TG >200 mg/dl, and HDL-C <40 mg/dl)	12 weeks	Lipid and lipoprotein profiles	Fenofibrate + simvastatin significantly reduced dense VLDL-C compared to fenofibrate (P<0.001) and simvastatin (P<0.0001). Simvastatin significantly reduced IDL-C compared with fenofibrate (P<0.003). The percentage of LDL-C pattern B constituting total LDL cholesterol was significantly reduced by fenofibrate (-13.7%, P<0.0001) and fenofibrate + simvastatin (-11.1%, P<0.0001). There was no significant change with simvastatin (-2.4%, P=0.27). Fenofibrate and fenofibrate + simvastatin significantly increased the percentage of buoyant LDL cholesterol constituting total LDL cholesterol (-19.6%, P<0.0001 and -16.9%, P<0.0001, respectively). There was no significant change with simvastatin (-3.1%, P=0.06).
Roth et al.[43] (2009) <u>Phase I</u> Fenofibrate 130 mg (FENO) and omega-3 acid ethyl esters 4 g (P-OM3) once daily for 8 weeks vs fenofibrate 130 mg (FENO) once daily and placebo for 8 weeks <u>Phase II</u>	RCT, DB, PC, MC Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300 mg/dl,	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After 8 weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (P=0.059). There was no significant difference between the treatment groups (P=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to FENO monotherapy (+48.2% vs +39.0%, respectively; P=0.030). There was no significant difference in non-HDL-C among the treatment groups (-8.2% for P-OM3 + FENO vs -7.1% for FENO; P=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6% vs -47.6%, respectively; P=0.016). There was a greater reduction in remnant like particle cholesterol (RLP-C) with P-OM3 + FENO than with FENO monotherapy (-72.0% vs -62.1%; P=0.029).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 130 mg (FENO) and omega-3 acid ethyl esters 4 g (P-OM3) once daily for 8 weeks				In the first 8-week extension study, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the double-blind treatment period (-17.5%, P=0.003). In the first 8-week extension study, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; P=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-15.4%, P=0.030 and -25.8%, P=0.035, respectively). There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the open-label phase of the study. In the pooled analysis of all patients enrolled in the 8-week open-label extension phase, the overall reductions of TGs and VLDL-C were -60.0% and -56.5%, respectively (both P<0.001). Non-HDLC and TC were also significantly reduced (P<0.001) over the 16-week treatment period in the pooled analysis. LDL-C increased +52.2% (P<0.001). There was no significant change in apolipoprotein B at the end of the 16-week treatment study (P=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events (AEs) were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis, dyspepsia, and headache.
Jones et al.[33] (2009) Fenofibric acid 135 mg and rosuvastatin (10 mg or 20 mg) once daily	MC, RCT, DB, AC Patients >18 years of age with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL	N=1,445 12 weeks	Primary: Mean percent change in HDL-C and TG (fenofibric acid plus rosuvastatin vs rosuvastatin), and LDL-C (fenofibric acid plus	Primary: Fenofibric acid plus rosuvastatin 10 mg resulted in a greater mean percent increase in HDL-C compared to rosuvastatin 10 mg (20.3% vs 8.5%, P<0.001) and a greater mean percent decrease in TGs (−47.1% vs −24.4%, P<0.001). Fenofibric acid plus rosuvastatin 10 mg resulted in a greater mean percent decrease in LDL-C compared to fenofibric acid monotherapy (−37.2% vs −6.5%, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fenofibric acid 135 mg once daily vs rosuvastatin (10 mg, 20 mg or 40 mg) once daily			rosuvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, total cholesterol (TC), apo B, and high-sensitivity C-reactive protein (hsCRP)	Fenofibric acid plus rosuvastatin 20 mg resulted in a greater mean percent increase in HDL-C compared to rosuvastatin 20 mg (19.0% vs 10.3%, P<0.001) and a greater mean percent decrease in TGs (−42.9% vs −25.6%, P<0.001). Fenofibric acid plus rosuvastatin 20 mg resulted in a greater mean percent decrease in LDL-C compared to fenofibric acid monotherapy (−38.8% vs −6.5%, P<0.001). Secondary: Fenofibric acid plus rosuvastatin 10 mg resulted in significantly greater improvements in non-HDL-C compared to fenofibric acid (P<0.001) and rosuvastatin 10 mg monotherapy (P<0.001). Fenofibric acid plus rosuvastatin 10 mg also resulted in greater improvements in VLDL-C (P<0.001), apo B (P<0.001), and hsCRP (P=0.013) than rosuvastatin 10 mg monotherapy. Fenofibric acid plus rosuvastatin 20 mg significantly improved non-HDL-C compared to fenofibric acid monotherapy (P<0.001) and resulted in a greater improvement in VLDL-C and hsCRP compared to rosuvastatin 20 mg monotherapy (P=0.038 and P=0.010, respectively), with similar reductions in non-HDL-C, apo B, and TC.
Mohiuddin et al.[34] (2009) Fenofibric acid 135 mg plus simvastatin 20 to 40 mg once daily vs fenofibric acid 135 mg once daily	MC, RCT, DB, AC Patients >18 years of age, with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL	N=657 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus simvastatin vs simvastatin), and LDL-C (fenofibric acid plus simvastatin vs fenofibric acid) Secondary:	Primary: Fenofibric acid plus simvastatin 20 mg resulted in a greater mean percent increase in HDL-C compared to simvastatin 20 mg (17.8% vs 7.2%, P<0.001) and a greater mean percent decrease in TGs (−37.4% vs −14.2%, P<0.001). Fenofibric acid plus simvastatin 20 mg resulted in a greater mean percent decrease in LDL-C compared to fenofibric acid monotherapy (−24.0% vs −4.0%, P<0.001). Fenofibric acid plus simvastatin 40 mg resulted in a greater mean percent increase in HDL-C compared to simvastatin 20 mg (18.9% vs 8.5%, P<0.001) and a greater mean percent decrease in TGs (−42.7% vs −22.4%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 20 to 80 mg once daily			Mean percent change in non-HDL-C, VLDL-C, total cholesterol (TC), apo B, and high-sensitivity C-reactive protein (hsCRP)	P<0.001). Fenofibric acid plus simvastatin 40 mg resulted in a greater mean percent decrease in LDL-C compared to fenofibric acid monotherapy (−25.3% vs −4.0%, P<0.001). Secondary: Fenofibric acid plus simvastatin 20 mg resulted in significantly greater improvements in non-HDL-C compared to simvastatin 20 mg and fenofibric acid monotherapy, and in VLDL-C, TC, and apo B compared to simvastatin 20 mg (P<0.012). Fenofibric acid plus simvastatin 40 mg significantly improved non-HDL-C compared to fenofibric acid (P<0.001) and resulted in a greater reduction in VLDL-C (P=0.005) and similar reductions in non-HDL-C, apo B, and TC compared to simvastatin 40 mg. There was no significant difference in hsCRP between the treatment groups.
Goldberg et al.[35] (2009) Fenofibric acid 135 mg plus atorvastatin 20 to 40 mg once daily vs fenofibric acid 135 mg once daily vs atorvastatin 20 to 40 mg once daily	MC, RCT, DB, AC Patients >18 years of age, with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL ≥130 mg/dl	N=613 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus atorvastatin vs atorvastatin), and LDL-C (fenofibric acid plus atorvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, total cholesterol (TC),	Primary: Fenofibric acid plus atorvastatin 20 mg resulted in a greater mean percent increase in HDL-C compared to atorvastatin 20 mg (14.0% vs 6.3%, P=0.005) and a greater mean percent decrease in TGs (-45.6% vs -16.5%, P<0.001). Fenofibric acid plus atorvastatin 20 mg resulted in a greater mean percent decrease in LDL-C compared to fenofibric acid monotherapy (-33.7% vs -3.4%, P<0.001). Fenofibric acid plus atorvastatin 40 mg resulted in a greater mean percent increase in HDL-C compared to atorvastatin 40 mg (12.6% vs 5.3%, P=0.010) and a greater mean percent decrease in TGs (-42.1% vs -23.2%, P<0.001). Fenofibric acid plus atorvastatin 40 mg resulted in a greater mean percent decrease in LDL-C compared to fenofibric acid monotherapy (-35.4% vs -3.4%, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			apo B, and high-sensitivity C-reactive protein (hsCRP)	Secondary: Fenofibric acid plus atorvastatin 20 mg resulted in significantly greater improvements in non-HDL-C compared to atorvastatin 20 mg (P=0.026) and fenofibric acid monotherapy (P<0.001), and in VLDL compared to atorvastatin 20 mg (P<0.001). More improvement in apolipoprotein B was observed with fenofibric acid plus atorvastatin 20 mg compared with atorvastatin 20 mg (P=0.046). Treatment with fenofibric acid plus atorvastatin 40 mg resulted in a significantly higher mean percentage of decrease in non–HDL cholesterol compared with fenofibric acid monotherapy (P<0.001) and a higher decrease in VLDL cholesterol compared with atorvastatin 40 mg monotherapy (P<0.001). Improvements in other secondary variables, such as total cholesterol and high-sensitivity C-reactive protein, were similar between combination therapy and atorvastatin monotherapy.
Jones et al.[36] (2009) Fenofibric acid 135 mg once daily vs low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) once daily vs fenofibric acid	MC, RCT, DB, AC (Pooled analysis of 3 trials) Patients >18 years of age, with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL ≥130 mg/dl	N=2715 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus atorvastatin vs atorvastatin), and LDL-C (fenofibric acid plus atorvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, total cholesterol (TC),	Primary: Fenofibric acid + low-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (18.1% vs 7.4%, P<0.001) and a greater mean percent decrease in TG (–43.9% vs -16.8%, P<0.001) compared to low-dose statin monotherapy, and a greater mean percent decrease in LDL-C (–33.1% vs -5.1%, P<0.001) compared to fenofibric acid monotherapy. Fenofibric acid + moderate-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (17.5% vs 8.7%, P<0.001) and a greater mean percent decrease in TG (–42.0% vs -23.7%, P<0.001) compared to moderate-dose statin monotherapy, and a greater mean percent decrease in LDL-C (–34.6% vs -5.1%, P<0.001) compared to fenofibric acid monotherapy. No formal comparisons were made between the high-dose statin monotherapy group and the other treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
135 mg plus low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) once daily vs moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) once daily vs fenofibric acid 135 mg plus moderate-dose statin once daily vs high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg)			apo B, high-sensitivity C-reactive protein (hsCRP), safety	Secondary: Greater improvements in non–HDL-C, VLDL-C, total cholesterol, and Apo-B were observed for fenofibric acid + low-dose statin combination therapy compared to corresponding monotherapies (P≤0.001). Combination therapy was generally well tolerated, and safety profiles were similar to monotherapies. No rhabdomyolysis was reported.
Bays et al.[37] (2008) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin	OL, MC Patients with mixed dyslipidemia completing one of three multicenter, prospective, double-	N=2,201 1 year	Primary: Safety, percent changes from baseline in TG, HDL-C, and LDL-C	Primary: Of the 2,201 patients who received at least one dose of fenofibric acid plus statin combination therapy, six patients (0.3%) died during the conduct of the extension study; no death was considered by the investigator to be treatment related. Overall, 148 (6.7%) patients had treatment-emergent serious adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg, simvastatin 40 mg, or atorvastatin 40 mg) Extension study patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated	blind, randomized, controlled, 12-week studies were eligible		Secondary: Percent changes in non–HDL-C, VLDL-C, TC, Apo-B, and hs-CRP levels	events (fenofibric acid + rosuvastatin, 7.2%; fenofibric acid + simvastatin, 7.8%; fenofibric acid + atorvastatin 4.6%). The most common treatment-emergent serious adverse events were osteoarthritis, deep vein thrombosis, coronary artery disease, myocardial infarction, and chest pain, diverticulitis, syncope, and intervertebral disc protrusion. A total of 1,856 patients (84.3%) had one or more treatment-emergent adverse events (fenofibric acid + rosuvastatin, 83.1%; fenofibric acid + simvastatin, 86.2%; fenofibric acid + atorvastatin, 85.2%). The most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, and back pain. Among patients who received fenofibric acid monotherapy in a controlled study, treatment with fenofibric acid + moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-22.0%), mean percent decrease in LDL-C (-38.1%), and mean percent increase in HDL-C (6.2%). Among patients who received moderate-dose statin monotherapy in a controlled study, treatment with fenofibric acid + moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-30.5%) and mean percent increases in HDL-C (13.1%) and LDL-C (3.1%). Among patients who received fenofibric acid + low-dose statin combination therapy in a controlled study, there was an additional median percent decrease in TG (-4.2%), mean percent increase in HDL-C (4.8%), and mean percent decrease in LDL-C (-9.7%) after the statin dose was increased for 52 weeks. The group of patients who were treated with fenofibric acid + moderate-dose statin in a controlled study and continued the same therapy in the extension study exhibited sustained improvements in lipid parameters throughout the course of therapy. For this group of patients, treatment with fenofibric acid + moderate-dose statin combination therapy for a total of 64 weeks decreased TG from a mean baseline of 297.8 mg/dL to a mean final level of 138.0 mg/dL, decreased LDL-C from a mean baseline of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				153.1 mg/dL to a mean final level of 94.2 mg/dL, and increased HDL-C from a mean baseline of 38.2 mg/dL to a mean final level of 47.7 mg/dL. Secondary: Among patients who received fenofibric acid monotherapy or moderate-dose statin monotherapy in the controlled studies, treatment with fenofibric acid + moderate-dose statin combination therapy in the extension study resulted in additional mean percent decreases in non–HDL-C, VLDL-C, TC, and Apo-B, and median percent decrease in hs-CRP that were sustained throughout 52 weeks of combination therapy. For patients initially treated with fenofibric acid + low-dose statin combination therapy, increasing the statin dose resulted in additional mean percent decreases in non–HDL-C, TC, and Apo-B and median percent decrease in hs-CRP, which were sustained throughout the study.
Kipnes et al.[18] (2010) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) Extension study patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated.	OL, MC Patients with mixed dyslipidemia completing one of three multicenter, prospective, double-blind, randomized, controlled, 12-week studies were eligible	N=310 2 years	Primary: Adverse events (AEs), percent changes from baseline in TG, HDL-C, and LDL-C	Primary: No death occurred during the second year of the study. Investigator-reported serious AEs occurred in 14.9% of patients in the fenofibric acid + rosuvastatin group compared to 8.0% with fenofibric acid + simvastatin and 5.8% with fenofibric acid + atorvastatin. There was no significant difference among the treatment groups. The incidence of AEs was similar among the treatment groups (94.8% with fenofibric acid + rosuvastatin, 90.0% with fenofibric acid + simvastatin, and 97.7% with fenofibric acid + atorvastatin). The most common treatment-related AEs were muscle spasms (3.9%), increased blood creatine phosphokinase (3.5%), headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported in any group. For patients taking open-label fenofibric acid + moderate-dose statin, the mean percentage changes from baseline to week 116 in efficacy variables were: +17.4% (HDL-C), -46.4% (TG), -40.4% (LDL-C), -47.3% (non-HDL-C), -37.8% (total-C) and -52.8% (VLDL-C).
Insua et al.[31]	DB, DD, R, XO	N=21	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Gemfibrozil 900 mg daily vs fenofibrate 200 mg QD	Patients between the ages of 45 and 70 years with primary hyperlipo-proteinemia, Fredrickson phenotypes IIa and IIb	6 weeks	Cholesterol-lowering effectiveness	Both drugs significantly reduced TC, calculated LDL-C, TG, apo B, and fibrinogen (P<0.01 for all calculations, except P<0.05 for fibrinogen with gemfibrozil therapy) and increased HDL-C (P<0.01). Neither drug affected Lp (a) lipoprotein, whereas uric acid was reduced only by fenofibrate (P<0.01). The percentage decrease in TC and LDL cholesterol was greater with fenofibrate than with gemfibrozil (–22% versus –15%; P<0.02; and –27% versus –16%; P<0.02, respectively). In contrast, reductions in levels of TG (–54% vs –46.5%), apo B, and fibrinogen, as well as the increase in HDL (+9% for both drugs), showed no significant difference between treatments. Separate analysis of patients with type IIb hyperlipoproteinemia showed essentially the same plasma lipid changes as for the overall group, but with greater modifications in TG and HDL concentrations.
Corbelli et al.[32] (2002) Gemfibrozil (mean daily dose 1,200 mg/day) vs fenofibrate (mean daily dose of 201 mg/day)	RETRO Patients who were switched from gemfibrozil to fenofibrate, due to inadequate lipid response or adverse effects	N=92 23 months	Primary: Mean TC, TG, HDL, and non-HDL	Primary: Compared to gemfibrozil, patients showed statistically significant improvements in mean TC, TG, HDL, and non-HDL (P<0.005). Specifically, more patients achieved a TG goal <200 mg/dL with fenofibrate (64%) compared to gemfibrozil (39%; P<0.0005). The study demonstrated that patients switched from gemfibrozil to fenofibrate due to an inadequate lipid response experienced significant improvements in lipid parameters for up to 18 months.
Primary Prevention of CHD Events				
Keech et al.[19] (2005) FIELD Fenofibrate 200 mg QD	DB, PC, R Patients aged 50-75 years with type 2 diabetes mellitus	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI) Secondary: Total	Primary: Coronary events occurred in 5.9% of patients on placebo and 5.2% of patients on fenofibrate (HR, 0.89; 95% CI, 0.75 to 1.05; P=0.16). There was a 24% reduction in nonfatal myocardial infarction with fenofibrate (HR, 0.76; 95% CI, 0.62 to 0.94; P=0.010).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			cardiovascular events which included the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization; total mortality	There was a nonsignificant increase in coronary heart disease mortality (HR, 1.19; 95% CI, 0.90 to 1.57; P=0.22). Secondary: Total cardiovascular disease events were significantly reduced from 13.9% to 12.5% with fenofibrate (HR, 0.89; 95% CI, 0.80 to 0.99; P=0.035). There was a 21% reduction in coronary revascularization with fenofibrate (HR, 0.79; 95% CI, 0.68 to 0.93; P=0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (P=0.18).
DAIS[20] (2001) Micronized fenofibrate 200 mg QD vs placebo	PC, R Men and women with type 2 diabetes with good glycemic control, who had mild lipoprotein abnormalities typical of type 2 diabetes and at least one visible coronary lesion	N=418 3 years	Primary: Mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter	Primary: Plasma TC, HDL-C, LDL-C, and TG concentrations all changed significantly more from baseline in the fenofibrate group (N=207) than in the placebo group (N=211). The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean 2.11 vs 3.65; P=0.02), a significantly smaller decrease in minimum lumen diameter (–0.06 vs –0.10 mm; P=0.029), and an insignificant smaller decrease in mean segment diameter (–0.06 vs –0.08 mm; P=0.171). The trial was not powered to examine clinical end points.
Frick et al.[21] (1987) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, R Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non–HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements)	N=4,081 5 years	Primary: Risk of CHD measured by incidence of cardiac events Secondary: Total mortality	Primary: There were minimal changes in serum lipid levels in the placebo group. The cumulative rate of cardiac end points at five years was 27.3 per 1,000 in the gemfibrozil group and 41.4 per 1,000 in the placebo group, a reduction of 34% in the incidence of CAD (95% CI, 8.2 to 52.6; P<0.02; two-tailed test). The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. Secondary: There was no difference between the groups in the total death rate, nor did the treatment influence the cancer rates.
Frick et al.[22]	DB, R	N=311	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1993) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	Individuals who exhibited symptoms and signs of possible CHD during screening in the Helsinki Heart Study	5 years	Risk of CAD measured by incidence of cardiac events Secondary: Total mortality	The end point rate, consisting of fatal and nonfatal MI and cardiac death, did not differ significantly between the placebo and gemfibrozil groups. Since there were key prognostic factors missing (e.g., true prevalence of CHD, extent of coronary artery obstructions, degree of left ventricular dysfunction, and their distribution in the groups render the results less reliable), the data cannot be used to refute the thesis that treatment of dyslipidemia in manifest CHD is successful. Secondary: Total mortality did not differ significantly between the placebo and gemfibrozil groups.
Heinonen et al.[23] (1994) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, MC Asymptomatic middle-aged men (40 to 55 years of age) with non–HDL-C greater than or equal to 200 mg/dL in 2 consecutive pretreatment measurements)	N=2,046 3.5 years	Primary: Definite fatal and nonfatal CHD events	Primary: During the post-trial period the numbers of definite CHD events in both groups (54 vs 47; P=NS) were smaller than expected without treatment, namely a reduction of around 40% for the original treatment groups. The mean incidence rates were in fact similar to that in the placebo group 5 years earlier. Cardiovascular mortality over the entire study period was similar but all-cause mortality was slightly higher among men of the original gemfibrozil group compared to the placebo group men (P=0.19).
Robins et al.[24] (2001) VA-HIT Gemfibrozil 1,200 mg daily vs placebo	DB, MC, PC, R Men with a history of CHD who had low HDL-C levels and low LDL-C levels	N=2,531 7 years	Primary: Nonfatal MI or death from coronary causes	Primary: Compared to placebo, gemfibrozil showed a 22% decreased risk of nonfatal MI or death due to CHD (17.3% gemfibrozil vs 21.7% placebo; P=0.006). Compared to placebo, gemfibrozil showed a 24% decreased risk for nonfatal MI, death due to CHD or confirmed stroke (20% gemfibrozil vs 26% placebo; P<0.001). A nonsignificant difference was seen in all-cause mortality with gemfibrozil compared to placebo (15.7% gemfibrozil vs 17.4% placebo; P=0.23). Concentrations of HDL-C were inversely related to CHD events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Multivariable Cox proportional hazards analysis showed that CHD events were reduced by 11% with gemfibrozil for every 5 mg/dL (0.13 mmol/L) increase in HDL-C (P=0.02). Events were reduced even further with gemfibrozil beyond that explained by increases in HDL-C values, particularly in the second through fourth quintiles of HDL-C values during treatment. During gemfibrozil treatment, only the increase in HDL-C significantly predicted a lower risk of CHD events; according to multivariable analyses, neither TG nor LDL-C levels at baseline or during the trial predicted CHD events.

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MC=multicenter, PA=parallel arm, PC=placebo controlled, R=randomized, RCT=randomized controlled trial, RETRO=retrospective study, XO=crossover
Miscellaneous abbreviations: apo=apolipoprotein, CHD=coronary heart disease, DAIS=Diabetes Atherosclerosis Intervention Study, FIELD=Fenofibrate Intervention and Event Lowering in Diabetes, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, ICAM-1=intercellular adhesion molecule-1, LDL=low-density lipoprotein, LDL-C=LDL cholesterol, MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, non–HDL-C=non–high-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, TRIMS=Triglyceride Reduction in Metabolic Syndrome, VA-HIT=Veterans Affairs High-Density Lipoprotein Intervention Trial, VCAM-1=vascular cell adhesion molecule-1, VLDL=very low-density lipoprotein, VLDL-C=very low-density lipoprotein cholesterol

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Fibric Acid Derivatives

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fenofibrate	capsule, tablet	Fenoglide®, Lipofen®, Lofibra®*	$$-$$$$	$-$$$
Fenofibrate, micronized	capsule	Antara®, Lofibra®*	$$-$$$$	$-$$$
Fenofibrate, nanocrystallized	tablet	Tricor®, Triglide®	$$-$$$$	N/A
Fenofibric acid	delayed-release capsule, tablet	Fibricor®*, Trilipix®	$$-$$$$	$-$$$
Gemfibrozil	tablet	Lopid®*	$$$	$

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

X. Conclusions

The fibric acid derivatives are approved for the treatment of hypertriglyceridemia, primary hypercholesterolemia and mixed dyslipidemia. They decrease triglycerides by 20% to 50% and increase HDL-C by 10% to 35%.[13] They can also lower LDL-C by 5% to 20%; however, LDL-C may increase in patients with hypertriglyceridemia. All of the fibric acid derivatives are available in a generic formulation, with the exception of the nanocrystallized formulation of fenofibrate (Tricor®).

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes (TLC).[12-17] Fibric acid derivatives have an adjunctive role in the treatment of patients with high triglycerides and low HDL-C, especially in combination with a statin.[12-15] For patients with very high triglycerides (≥500 mg/dl), treatment with a fibric acid derivative or niacin should be implemented before LDL-lowering therapy to prevent pancreatitis. Guidelines do not give preference to one fibric acid derivative over another.

Clinical trials have demonstrated that the fibric acid derivatives can effectively lower triglycerides and increase HDL-C, as well as positively impact other lipid/lipoprotein parameters. Complementary lipid effects were also observed in clinical trials when fibric acid derivatives were coadministered with ezetimibe and statins.[18,28-30,33-36,38,41-42,44-45] However, the effect of fibric acid derivatives on cardiovascular morbidity and mortality has not been determined.[4-11] In the FIELD study, fenofibrate was associated with a non-significant reduction in coronary heart disease events in patients with type 2 diabetes, as well as a non-significant increase in total and coronary heart disease mortality.[4-11,19] In the Coronary Drug Project, there was no difference in mortality with clofibrate in patients with a history of myocardial infarction.[4-11] In a study conducted by the World Health Organization, there was a significant increase in all-cause mortality with clofibrate in patients without coronary heart disease.[4-11] In the Helsinki Heart Study, gemfibrozil was associated with a non-significant increase in total mortality in patients without coronary heart disease.[4-11,21] There was also a non-significant increase in cardiac deaths with gemfibrozil in a secondary prevention component of the Helsinki Heart Study.[4-11,22] Because of chemical, pharmacological, and clinical similarities between the fibric acid derivatives, the findings from these studies may apply to all of the agents in this class.[4-11]

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

Therefore, all brand fibric acid derivatives 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 fibric acid derivative 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 HMG-CoA Reductase Inhibitors
AHFS Class 240608
August 11, 2010

I. Overview

The antilipemic agents are categorized into 5 different AHFS classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their FDA-approved indications, mechanism of action, efficacy, safety profiles, tolerability and ease of use.

The HMG-CoA reductase inhibitors (statins) include single entity agents (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin), as well as fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/simvastatin, niacin/lovastatin and niacin/simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis.[4-14] This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of LDL-C receptors. Statins also decrease the release of lipoproteins from the liver. The statins are by far the most effective class of drugs to lower LDL-C. Depending on the agent selected, the statins can decrease LDL-C by 18% to 60% when used as monotherapy.[17,20] The effects on LDL-C are dose-dependent and log-linear. There is an additional 6% reduction in LDL-C with each doubling of the dose. The statins also decrease triglycerides by 7% to 30% and increase HDL-C by 5% to 15%.[17]

Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.[6] The exact mechanism by which niacin alters lipids is not completely understood. It may inhibit the mobilization of free fatty acids from adipose tissue, decrease the delivery of free fatty acids to the liver, decrease triglyceride synthesis, alter the hepatic production of apolipoprotein B, and increase HDL-C by reducing its catabolism.[10-11] Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension, chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease.[4]

The HMG-CoA reductase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The lipid-lowering effects of the statins are noted in Table 2. Lovastatin, pravastatin and simvastatin are available in a generic formulation. Pitavastatin (Livalo®) was recently added to Medicaid's drug file in May 2010 and will not be included in this review. Alabama Medicaid's policy states that drugs must be commercially available for a minimum of 180 days to be eligible for inclusion in a PDL review. This class was last reviewed in May 2008.

Table 1. HMG-CoA Reductase Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amlodipine and atorvastatin	tablet	Caduet®	none
Atorvastatin	tablet	Lipitor®	none
Ezetimibe and simvastatin	tablet	Vytorin®	none
Fluvastatin	capsule, extended-release tablet	Lescol®, Lescol XL®	Lescol®, Lescol XL®
Lovastatin	extended-release tablet, tablet	Altoprev®, Mevacor®*	lovastatin
Niacin and lovastatin	extended-release tablet	Advicor®	none
Niacin and simvastatin	extended-release tablet	Simcor®	none
Pravastatin	tablet	Pravachol®*	pravastatin
Rosuvastatin	tablet	Crestor®	none
Simvastatin	tablet	Zocor®*	simvastatin

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

Table 2. Lipid-lowering Effects of the HMG-CoA Reductase Inhibitors*[1-14]

Generic Name(s)	Total-C ↓ (%)	LDL-C ↓ (%)	Triglycerides ↓ (%)	HDL-C ↑ (%)
Atorvastatin	25-58	27-60	17-53	5-14
Ezetimibe and simvastatin	31-43	45-60	23-31	6-10
Fluvastatin	16-25	22-38	12-25	2-11
Lovastatin	16-34	21-42	10-27	5-12
Niacin and lovastatin	Not reported	30-42	32-44	20-30
Niacin and simvastatin†	2-11	5-14	22-38	8-19
Pravastatin	16-33	22-41	10-24	1-14
Rosuvastatin	24-46	28-63	10-43	3-22
Simvastatin	19-52	26-51	8-41	7-16

*Includes studies in the prescribing information. Data are mean changes from baseline; data are pooled from different studies and may not be directly comparable.
†Patients were receiving simvastatin 20-40 mg at baseline.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the HMG-CoA reductase inhibitors are summarized in Table 3. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 3. Treatment Guidelines Using the HMG-CoA Reductase Inhibitors

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[16] (2004)**	General Recommendations • Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. Heterozygous Familial Hypercholesterolemia • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins: first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid). Homozygous Familial Hypercholesterolemia • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). Familial Defective Apolipoprotein B-100 (FDB)

Clinical Guideline	Recommendation(s)
	• TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. Polygenic Hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP). **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report[17] (2002)**	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies[18] (2007)**	• Statins are considered first-line drugs for lowering LDL-C. • When TG are between ~450-900 mg/dL, statins (or fibrates) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update[19] (2006)**	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Lipid Management in Adults[20] (2009)**	• For monotherapy, statins are the drugs of choice for lowering LDL. • If patients are unable to take statins, then bile-acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile-acid sequestrant, with fewer side effects.

Clinical Guideline	Recommendation(s)
	• In very resistant cases, triple therapy may be needed.
National Institute for Health and Clinical Excellence (NICE): **Lipid Modification[21] (2008)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a ≥20% 10-year risk of developing CVD. • Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of CVD. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of CVD. • Statin therapy is recommended for adults with clinical evidence of CVD. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dl) or LDL-C <2 mmol/L (<77 mg/dl) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association[192] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
American Heart Association (AHA)/American Stroke Association (ASA): **Primary Prevention of Ischemic Stroke[193] (2006)**	• Patients with known CAD and high-risk hypertensive patients (even with normal LDL cholesterol levels) should be treated with lifestyle measures and a statin. • For patients with low HDL-C, consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL. • For patients with elevated Lp[a], consider niacin (immediate- or extended-release formulation) in conjunction with glycemic control and LDL-C control.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the HMG-CoA reductase inhibitors 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 HMG-CoA Reductase Inhibitors[1-14]

Indication	Amlodipine/ Atorvastatin†	Atorva-statin	Ezetimibe/ Simvastatin	Fluva-statin	Lova-statin	Niacin/ Lovastatin§	Niacin/ Simvastatin‡	Prava-statin	Rosuva-statin	Simva-statin
Hypertriglyceridemia										
Adjunct to diet for the treatment of patients with elevated serum triglyceride levels	✔	✔						✔	✔	✔
Adjunct to diet to reduce triglycerides in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate							✔			
Treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.*						✔				
Primary Hypercholesterolemia and Mixed Dyslipidemia										
Adjunct to diet to reduce elevated total-C, LDL-C, apo B, and triglyceride levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb)	✔	✔		✔		✔		✔		✔
Adjunct to diet for the reduction of elevated total-C, LDL-C, Apo B, triglycerides, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia			✔						✔	
Adjunct to diet to reduce total-C, LDL-C, Apo B, non-HDL-C, or triglycerides, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson type IIa and IIb) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate							✔			

Indication	Amlodipine/ Atorvastatin†	Atorva-statin	Ezetimibe/ Simvastatin	Fluva-statin	Lova-statin	Niacin/ Lovastatin§	Niacin/ Simvastatin‡	Prava-statin	Rosuva-statin	Simva-statin
Adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb)					✔	✔				
Adjunct to diet to reduce total-C, LDL-C, and Apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: 1) LDL-C remains ≥190 mg/dL or 2) LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present	✔	✔			✔				✔	✔
Adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-16 years of age, with heterozygous familial hypercholesterolemia whose response to dietary restriction has not been adequate and the following findings are present: 1) LDL-C remains ≥190 mg/dL or 2) LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular disease risk factors are present				✔						
Adjunct to diet for treatment of heterozygous familial hypercholesterolemia in children and adolescent patients ages 8 years and older if after an adequate trial of diet the following findings are present: 1) LDL-C remains ≥190 mg/dL or 2) LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the patient								✔		
Adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia	✔	✔						✔	✔	✔
Adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia	✔	✔	✔							✔
Adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, total-C and Apo B in adult patients with homozygous familial hypercholesterolemia									✔	

Indication	Amlodipine/ Atorvastatin†	Atorva-statin	Ezetimibe/ Simvastatin	Fluva-statin	Lova-statin	Niacin/ Lovastatin§	Niacin/ Simvastatin‡	Prava-statin	Rosuva-statin	Simva-statin
Primary Prevention of Cardiovascular Disease										
Reduce the risk of myocardial infarction, stroke, revascularization procedures and angina in adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease		✔								
Reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension		✔								
Reduce the risk of myocardial infarction, unstable angina, and coronary revascularization procedures in individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C					✔					
Reduce the risk of myocardial infarction, the risk of undergoing myocardial revascularization, procedures, and the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes in hypercholesterolemic patients without clinically evident coronary heart disease								✔		
Reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in individuals without clinically evident coronary heart disease, but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and the presence of at least 1 additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease									✔	
Reduce the risk of total mortality by reducing CHD 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										✔

Indication	Amlodipine/ Atorvastatin†	Atorva-statin	Ezetimibe/ Simvastatin	Fluva-statin	Lova-statin	Niacin/ Lovastatin§	Niacin/ Simvastatin‡	Prava-statin	Rosuva-statin	Simva-statin
Secondary Prevention of Cardiovascular Disease										
Reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF and angina in patients with clinically evident coronary heart disease		✔								
Reduce the risk of undergoing coronary revascularization procedures in patients with coronary heart disease				✔						
Reduce the risk of total mortality by reducing coronary death, as well as reduce the risk of myocardial infarction, stroke and stroke/transient ischemic attack, risk of undergoing myocardial revascularization procedures								✔		
Reduce the risk of total mortality by reducing coronary heart disease deaths, reduce the risk of non-fatal myocardial infarction and stroke, reduce the need for coronary and non-coronary revascularization procedures in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease										✔
Slow the progression of coronary atherosclerosis in patients with coronary heart disease				✔	✔			✔	✔	
Miscellaneous										
Treatment of hypertension, chronic stable angina, vasospastic angina, or angiographically documented coronary artery disease	✔									

†For use when treatment with both amlodipine and atorvastatin is appropriate.
§For use when treatment with both niacin extended-release and lovastatin is appropriate.
‡For use when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.
*Such patients typically have serum triglyceride levels over 2000 mg/dL and have elevations of VLDL-C as well as fasting chylomicrons (Type V hyperlipidemia). Patients who consistently have total serum or plasma TG below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with niacin may be considered for those patients with TG elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis.

IV. Pharmacokinetics

The pharmacokinetic parameters of the HMG-CoA reductase inhibitors are listed in Table 5. All statins undergo extensive first-pass metabolism, resulting in relatively low bioavailability following oral administration. However, the hepatic HMG-CoA inhibition occurs as a result of the high liver concentrations during first-pass metabolism. Thus, their therapeutic effect is not lessened by this high first-pass extraction.

Table 5. Pharmacokinetic Parameters of the HMG-CoA Reductase Inhibitors[1-14]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amlodipine and atorvastatin	AM: 64-90 AT: 14	AM: 93 AT: 98	AM: Liver (90) AT: Liver	AM: Renal (10-60) AT: Renal (<2)	AM: 30-50 AT: 14
Atorvastatin	14	98	Liver	Renal (<2)	7-14
Ezetimibe and simvastatin	E: NR S: <5	E: >90 S: 95	E: Liver, Small intestine S: Liver	E: Renal (11) Feces (78) S: Renal (13) Feces (60)	E: 22 S: NR
Fluvastatin	20-30	98	Liver	Renal (5) Feces (95)	<3
Lovastatin	5	>95	Liver	Renal (10) Feces (83)	NR
Niacin and lovastatin	N: 60-76 L: 5	N: 20 L: >95	N: Liver L: Liver	N: Renal (50) L: Renal (10) Feces (83)	N: <1 L: 4.5
Niacin and simvastatin	N: 60-76 S: <5	N: NR S: NR	N: Liver S: Liver	N: Renal (53-77) S: Renal (13) Feces (60)	N: NR S: 4.2-4.9
Pravastatin	17	43-55	Liver	Renal (20) Feces (37)	2.6-3.2
Rosuvastatin	20	88	Liver, minimal	Renal (10) Feces (90)	19
Simvastatin	5	95	Liver	Renal (13) Feces (60)	S: NR

AM=amlodipine, AT=atorvastatin, E=ezetimibe, L=lovastatin, N=niacin, NR=not reported, S=simvastatin

V. Drug Interactions

Significant drug interactions with the HMG-CoA reductase inhibitors are listed in Table 6.

Table 6. Significant Drug Interactions with the HMG-CoA Reductase Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
HMG-CoA reductase inhibitors (lovastatin, simvastatin)	1	Amiodarone	Inhibition of cytochrome P450 isoenzymes by amiodarone may decrease the metabolic elimination of HMG-CoA reductase inhibitors. The pharmacologic effects of HMG-CoA reductase inhibitors may be increased by amiodarone. Elevated plasma concentrations with toxicity characterized by muscle injury may occur.
HMG-CoA reductase inhibitors (fluvastatin,	1	Anticoagulants	The hypoprothrombinemic effects of anticoagulants may be increased HMG-CoA reductase inhibitors. Hematuria,

Generic Name(s)	Significance Level	Interaction	Mechanism
lovastatin, rosuvastatin, simvastatin)			epistaxis and rectal bleeding may occur. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (all)	1	Cyclosporine	Cyclosporine may decrease the elimination of HMG-CoA reductase inhibitors by inhibiting their metabolism. Toxic effects of HMG-CoA reductase inhibitors including liver enzyme elevation, myopathy, and rhabdomyolysis may be increased by cyclosporine.
HMG-CoA reductase inhibitors (lovastatin, simvastatin)	1	Danazol	The risk of myopathy may be increased by concomitant use of danazol with HMG-CoA reductase inhibitors. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (all)	1	Daptomycin	Coadministration of daptomycin and HMG-CoA reductase inhibitors may increase the risk of rhabdomyolysis. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (atorvastatin, pravastatin, simvastatin)	1	Diltiazem	The inhibition of cytochrome P450 3A4 isoenzymes by diltiazem may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by co-administration of diltiazem. The risk of myopathy and rhabdomyolysis may be increased.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, simvastatin)	1	Efavirenz	Induction of cytochrome P450 3A4 isoenzymes by efavirenz may increase the metabolic elimination of HMG-CoA reductase inhibitors. Efavirenz may decrease plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (all)	1	Fibric acid derivatives	Coadministration of fibric acid derivatives with HMG-CoA reductase inhibitors may result in myopathy or rhabdomyolysis.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, simvastatin)	1	Fluconazole	Inhibition of cytochrome P450 3A4 isoenzymes by fluconazole may decrease the metabolic elimination of HMG-CoA reductase inhibitors. The risk of myopathy and rhabdomyolysis may be increased by coadministration of HMG-CoA reductase inhibitors and fluconazole.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, rosuvastatin, simvastatin)	1	HIV protease inhibitors	Inhibition of cytochrome P450 3A4 isoenzymes by HIV Protease Inhibitors may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Pharmacologic and toxic effects of HMG-CoA reductase inhibitors may be increased by HIV protease inhibitors.
HMG-CoA reductase	1	Imidazoles	Inhibition of cytochrome P450 3A4

Generic Name(s)	Significance Level	Interaction	Mechanism
inhibitors (atorvastatin, fluvastatin, lovastatin, simvastatin)			isoenzymes by imidazoles may decrease the metabolic elimination of HMG-CoA reductase inhibitors. The risk of myopathy and rhabdomyolysis may be increased by coadministration of HMG-CoA reductase inhibitors and imidazoles.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Macrolides and ketolides	Inhibition of cytochrome P450 3A4 isoenzymes by macrolides and ketolides may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Macrolides and ketolides may increase pharmacologic effects of HMG-CoA reductase inhibitors. Elevated plasma concentrations with toxicity characterized by liver enzyme elevation and myopathy may occur.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Nefazodone	Inhibition of cytochrome P450 3A4 isoenzymes by nefazodone may decrease the metabolic elimination of HMG-CoA reductase inhibitors. The risk of myopathy and rhabdomyolysis may be increased when HMG-CoA reductase inhibitors and nefazodone are coadministered.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Non-nucleoside reverse transcriptase inhibitors (NNRT inhibitors)	Inhibition of cytochrome P450 3A4 isoenzymes by NNRT inhibitors may decrease the metabolic elimination of HMG-CoA reductase inhibitors. NNRT inhibitors may increase plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
Amlodipine	2	HIV protease inhibitors	Inhibition of cytochrome P450 3A4 isoenzymes by HIV protease inhibitors may decrease the metabolic elimination of amlodipine, which may increase the antihypertensive effect of amlodipine.
Amlodipine	2	Imidazoles	Inhibition of cytochrome P450 3A4 isoenzymes by imidazoles may decrease the metabolic elimination of amlodipine. Imidazoles may increase the plasma concentrations and pharmacologic effects of amlodipine. Additionally, amlodipine and imidazoles can have additive negative inotropic effects increasing the risk of CHF.
Amlodipine	2	Vasopressin receptor antagonists	Inhibition of cytochrome P450 3A4 by vasopressin receptor antagonists may decrease the metabolic elimination of amlodipine. Plasma concentrations of amlodipine may be increased by co-administration of vasopressin receptor antagonists.
Atorvastatin	2	Quinine	Plasma concentrations of atorvastatin may be increased by co-administration of quinine. The risk of myopathy and/or rhabdomyolysis may be increased.

Generic Name(s)	Significance Level	Interaction	Mechanism
			Inhibition of atorvastatin first-pass metabolism via CYP3A4 by quinine is suspected.
Ezetimibe	2	Cyclosporine	When cyclosporine and ezetimibe are co-administered, exposure to both drugs may be increased potentially increasing the pharmacologic effects and adverse reactions. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Bosentan	Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by bosentan. Reduced therapeutic efficacy of HMG-CoA reductase inhibitors may occur. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Carbamazepine	Induction of cytochrome P450 3A4 metabolism by carbamazepine may cause increased metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by carbamazepine.
HMG-CoA reductase inhibitors (all)	2	Colchicine	The combination of HMG-CoA reductase inhibitors with colchicine may result in an increased potential for myopathy.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Dronedarone	Inhibition of CYP 3A isoenzymes and P-glycoprotein by dronedarone may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by dronedarone. Toxicity, characterized by muscle injury may occur.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Hypericum perforatum	Induction of intestinal and hepatic cytochrome P450 3A4 isoenzymes by hypericum perforatum may increase the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by hypericum perforatum.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Imatinib	Inhibition of cytochrome P450 3A4 isoenzymes by imatinib may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by imatinib.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Mibefradil	Use of HMG-CoA reductase inhibitors with mibefradil may increase the risk of adverse effects, including myopathy and rhabdomyolysis. The addition of tacrolimus or cyclosporine may further increase the potential to develop toxicity.

Generic Name(s)	Significance Level	Interaction	Mechanism
			The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Rifamycins	Induction of pre-hepatic and hepatic cytochrome P450 3A4-mediated metabolism by rifamycins may increase the metabolic elimination of HMG-CoA reductase inhibitors. Pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by rifamycins and impaired cholesterol-lowering efficacy may result.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, simvastatin)	2	Streptogramins	Inhibition of cytochrome P450 3A4 isoenzymes by streptogramins may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Streptogramins may increase the pharmacologic and toxic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Vasopressin receptor antagonists	Inhibition of cytochrome P450 3A4 by vasopressin receptor antagonists may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations of HMG-CoA reductase inhibitors may be increased by co-administration of vasopressin receptor antagonists.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Verapamil	Inhibition of cytochrome P450 3A4 isoenzymes by verapamil may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by verapamil. Toxicity, characterized by muscle injury, may occur.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Voriconazole	Inhibition of cytochrome P450 3A4 isoenzymes by voriconazole may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by voriconazole.
Rosuvastatin	2	Thrombopoietin mimetics	Inhibition of the organic anion transporting polypeptide OATP1B1 by thrombopoietin mimetics may increase the systemic exposure of rosuvastatin.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the HMG-CoA reductase inhibitors are listed in Table 7. These agents are generally well tolerated with only mild side effects, such as abdominal pain, constipation, flatulence and headache.[1-14] Myopathy has also been reported with the HMG-CoA reductase inhibitors, which can progress to rhabdomyolysis and acute renal failure. Risk factors for developing rhabdomyolysis include age >65 years, hypothyroidism, and poor renal function. Increases in hepatic transaminases >3 times the upper limit of normal have also been reported with the HMG-CoA reductase inhibitors.

Table 7. Adverse Drug Events (%) Reported with the HMG-CoA Reductase Inhibitors[1-14]

Adverse Events	Amlodipine/ Atorvastatin	Atorvastatin	Ezetimibe/ Simvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Niacin/ Lovastatin	Niacin/ Simvastatin	Pravastatin	Rosuvastatin	Simvastatin
Cardiovascular										
Arrhythmia	<1	-	-	-	-	✔	-	-	-	-
Atrial fibrillation	-	-	✔	-	-	✔	-	-	-	6
Bradycardia	<1	-	-	-	-	-	-	-	-	-
Cardiac failure	<1	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	<1‡	✔	-	4	-	-
Flushing	1-3	-	✔	✔	✔	71	59	<1	-	✔
Hypotension	<1	-	-	-	-	✔	✔	-	-	-
Orthostasis	-	-	-	-	-	✔	✔	-	-	-
Palpitation	1-4	-	-	-	-	✔	✔	-	-	-
Peripheral edema	2-15	-	-	-	-	-	-	-	-	-
Postural hypotension	<1	-	-	-	-	✔	-	-	-	-
Syncope	<1	-	-	-	-	✔	✔	-	-	-
Tachycardia	-	-	-	-	-	✔	-	-	-	-
Central Nervous System										
Abnormal dreams	<1	-	-	-	-	-	-	-	-	-
Agitation	<1	-	-	-	-	-	-	-	-	-
Amnesia	<1	-	-	-	-	-	✔	-	-	-
Anxiety	<1	-	-	✔	✔	✔	-	1	-	-
Apathy	<1	-	-	-	-	-	-	-	-	-
Ataxia	<1	-	-	-	-	-	-	-	-	-
Chills	-	-	✔	✔	✔	✔	✔	✔	-	✔
Cranial nerve dysfunction	-	-	-	✔	✔	-	-	✔	-	-
Depersonalization	<1	-	-	-	-	-	-	-	-	-
Depression	<2	<2	✔	✔	✔	-	-	1	-	✔
Dizziness	1-3	<2	✔	✔	<2	✔	-	1-3	4	✔
Emotional lability	<2	<2	-	-	-	-	-	-	-	-
Extrapyramidal symptoms	<1	-	-	-	-	-	-	-	-	-
Facial paralysis/paresis	-	-	-	✔	-	-	-	✔	-	-

Adverse Events	Amlodipine/ Atorvastatin	Atorvastatin	Ezetimibe/ Simvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Niacin/ Lovastatin	Niacin/ Simvastatin	Pravastatin	Rosuvastatin	Simvastatin
Fatigue	<4	<2	✔	3/2	-	-	-	4	-	-
Fever	-	-	✔	✔	✔	✔	✔	<1	-	✔
Headache	7	2-17	6	9/5	2-3/7	9	4-9	2-6	6-9	3
Incoordination	<2	<2	-	-	-	-	-	-	-	-
Insomnia	1-5	1-5	✔	3/<1	<1‡	✔	✔	1	-	4
Malaise	<2	<2	✔	✔	✔	✔	-	✔	-	✔
Memory impairment	<2	<2	✔	✔	✔	✔	✔	<1	✔	✔
Migraine	<2	<2	-	-	-	✔	-	-	-	-
Nervousness	-	-	-	-	-	✔	-	-	-	-
Nightmare	<2	<2	-	-	-	-	-	-	-	-
Paresthesia	<2	<2	✔	✔	<1‡	✔	-	<1	-	✔
Peripheral nerve palsy	✔	✔	-	✔	✔	-	-	✔	-	✔
Peripheral neuropathy	<2	<2	✔	✔	✔	✔	✔	<1	-	✔
Psychiatric disturbances	-	-	-	✔	✔	✔	-	-	-	-
Somnolence	1-2	-	-	-	-	-	-	-	-	-
Tremor	✔	✔	-	✔	✔	✔	-	<1	-	-
Vertigo	<1	✔	✔	✔	✔	✔	-	<1	-	5
Dermatologic										
Acanthosis nigricans	-	-	-	-	-	✔	-	-	-	-
Alopecia	<2	<2	✔	✔	<1‡	✔	-	<1	-	✔
Burning sensation	-	-	-	-	-	✔	-	-	-	-
Dry skin	-	-	-	✔	✔	✔	-	<1	-	✔
Ecchymosis	<2	<2	-	-	-	-	-	-	-	-
Eczema	-	-	✔	-	-	-	-	-	-	5
Erythema multiforme	<2	<2	✔	✔	✔	✔	✔	✔	-	✔
Exfoliative dermatitis	<1	-	-	-	-	-	-	-	-	-
Hyperpigmentation	-	-	-	-	-	✔	-	-	-	-
Pruritus	1-2	<2	✔	✔	<1‡	7	5	<1	✔	✔
Rash	1-2	<2	✔	-	1‡	5	✔	4	✔	✔
Skin discoloration	<1	-	-	-	-	-	✔	-	-	-
Stevens-Johnson syndrome	<2	<2	✔	✔	✔	✔	✔	✔	-	✔
Sweating	-	-	-	-	-	✔	-	-	-	-
Toxic epidermal necrolysis	<2	<2	✔	✔	✔	✔	✔	✔	-	✔
Urticaria	<2	<2	✔	✔	✔	✔	✔	<1	✔	✔
Endocrine and Metabolic										
Decreased glucose tolerance	-	-	-	-	-	✔	✔	-	-	-
Gout	-	-	-	-	-	✔	✔	-	-	-

Adverse Events	Amlodipine/ Atorvastatin	Atorvastatin	Ezetimibe/ Simvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Niacin/ Lovastatin	Niacin/ Simvastatin	Pravastatin	Rosuvastatin	Simvastatin
Thyroid dysfunction	✔	✔	-	-	-	-	-	✔	-	-
Gastrointestinal										
Abdominal pain	1-2	-	✔	5/4	2‡	4	4	2	2	6
Acid regurgitation	-	-	-	-	<1‡	-	-	-	-	-
Anorexia	-	-	-	✔	✔	✔	-	-	-	-
Biliary pain	<2	<2	-	-	-	-	-	-	-	-
Cholestasis	<2	<2	-	-	-	-	-	-	-	-
Colitis	<2	<2	-	-	-	-	-	-	-	-
Constipation	<2	<2	✔	-	2-3‡	✔	2	1-2	2-3	2
Diarrhea	5-14	5-14	3	5/3	2/3	6	2-7	6	-	✔
Decreased appetite	-	-	-	-	-	-	-	<1	-	-
Dry mouth	-	-	-	-	<1‡	✔	-	-	-	-
Duodenal ulcer	<2	<2	-	-	-	-	-	-	-	-
Dyspepsia	1-6	3-6	✔	8/4	1-2‡	3	4	3	-	✔
Dysphagia	<2	<2	-	-	-	-	-	-	-	-
Enteritis	-	-	-	-	-	-	-	-	-	-
Eructation	<2	<2	-	-	-	✔	-	-	-	-
Esophagitis	<2	<2	-	-	-	-	-	-	-	-
Flatulence	1-3	1-3	✔	3/1	3-4	✔	2	1-3	-	✔
Gastritis	<2	<2	✔	-	-	-	-	-	-	5
Gastroenteritis	<2	<2	-	-	-	-	-	-	-	-
Gingival hyperplasia	✔	-	-	-	-	-	-	-	-	-
Glossitis	<2	<2	-	-	-	-	-	-	-	-
Gum hemorrhage	<2	<2	-	-	-	-	-	-	-	-
Melena	<2	<2	-	-	-	-	-	-	-	-
Nausea	3-7	4-7	✔	3	2	7	5	7	2-6	✔
Pancreatitis	<2	<2	✔	✔	✔	✔	✔	✔	✔	✔
Peptic ulcer	-	-	-	-	-	✔	-	-	-	-
Rectal hemorrhage	<2	<2	-	-	-	-	-	-	-	-
Stomatitis	<2	<2	-	-	-	-	-	-	-	-
Tenesmus	<2	<2	-	-	-	-	-	-	-	-
Vomiting	<2	<2	✔	✔	<1‡	3	-	7	-	✔
Genitourinary										
Dysuria	-	-	-	-	-	-	-	<1	-	-
Erectile dysfunction	1-2	✔	-	✔	✔	✔	-	<1	-	-
Hematuria	<2	<2	-	-	-	-	-	-	✔	-
Libido decreased	-	-	-	✔	✔	✔	-	<1	-	-

Adverse Events	Amlodipine/ Atorvastatin	Atorvastatin	Ezetimibe/ Simvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Niacin/ Lovastatin	Niacin/ Simvastatin	Pravastatin	Rosuvastatin	Simvastatin
Metrorrhagia	<2	<2	-	-	-	-	-	-	-	-
Myoglobinuria	-	-	-	-	-	-	-	-	-	-
Nephritis	<2	<2	-	-	-	-	-	-	-	-
Nocturia	-	-	-	-	-	-	-	<1	-	-
Proteinuria	-	-	-	-	-	-	-	-	✔	-
Renal failure	-	-	-	-	-	-	-	-	✔	-
Urinary abnormality	-	-	-	-	-	-	-	<1	-	-
Urinary tract infection	4-8	4-8	✔	2/3	2†	-	-	-	-	3
Urinary urgency	-	-	-	-	-	-	-	1	-	-
Vaginal hemorrhage	<2	<2	-	-	-	-	-	-	-	-
Hematologic										
Eosinophilia	✔	✔	✔	✔	✔	✔	✔	✔	-	✔
ESR increased	-	-	✔	✔	✔	✔	✔	✔	-	✔
Hemolytic anemia	✔	✔	✔	✔	✔	✔	✔	✔	-	✔
Leukopenia	-	-	✔	✔	✔	✔	✔	✔	-	✔
Prothrombin time increased	-	-	-	-	-	-	✔	-	-	-
Thrombocytopenia	<2	<2	✔	✔	✔	✔	✔	✔	-	✔
Hepatic										
Cirrhosis	✔	✔	-	✔	✔	✔	-	✔	-	-
Fulminant hepatic necrosis	✔	✔	-	✔	✔	✔	-	✔	-	-
Hepatic failure	<2	<2	✔	-	-	-	✔	-	✔	✔
Hepatitis	<2	<2	✔	✔	✔	✔	✔	✔	✔	✔
Hepatoma	-	-	-	✔	✔	✔	-	✔	-	-
Jaundice	<2	<2	✔	✔	✔	✔	-	✔	✔	✔
Laboratory Test Abnormalities										
Alkaline phosphatase increased	<2	<2	✔	-	-	✔	✔	-	✔	✔
Amylase increased	-	-	-	-	-	✔	✔	-	-	-
Bilirubin increased	-	-	-	✔	✔	✔	✔	-	✔	-
Creatine kinase increased	<2	<2	✔	-	-	✔	✔	-	3	✔
Hyperglycemia	<2	<2	✔	-	-	4	✔	-	✔	4
Hypoglycemia	<2	<2	-	-	-	-	-	-	-	-
LDH increased	-	-	-	-	-	✔	✔	-	-	-
Positive antinuclear antibody	-	-	-	✔	✔	-	-	✔	-	✔
Proteinuria	-	-	-	-	-	-	-	-	✔	-
Thyroid function abnormalities	-	-	-	✔	✔	✔	✔	✔	✔	-

Adverse Events	Amlodipine/ Atorvastatin	Atorvastatin	Ezetimibe/ Simvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Niacin/ Lovastatin	Niacin/ Simvastatin	Pravastatin	Rosuvastatin	Simvastatin
Transaminases increased	<3	<3	4	✔	✔	✔	✔	1	2	✔
Uric acid increased	-	-	-	-	-	✔	✔	-	-	-
Musculoskeletal										
Arthralgia	4-12	4-12	✔	3†	<1/5	✔	✔	6	4-10	✔
Arthritis	-	-	✔	2/1	1-6/5	✔	✔	✔	-	✔
Asthenia	-	-	✔	✔	1-2/3	5	-	✔	1-5	✔
Back pain	-	-	-	-	5†	5	5	-	-	-
Bursitis	<2	<2	-	-	-	-	-	-	-	-
Dermatomyositis	✔	✔	✔	-	-	-	✔	✔	-	✔
Leg cramps	<2	<2	-	-	-	-	-	-	-	-
Leg pain	-	-	-	-	<1‡	-	-	-	-	-
Limb pain	3-9	3-9	-	-	-	-	-	-	-	-
Localized pain	-	-	-	-	-	-	-	1	-	-
Muscle cramps	1-2	-	✔	✔	<1‡	✔	-	2	-	✔
Muscle fatigue	<2	<2	-	-	-	-	-	-	-	-
Muscle spasms	2-5	2-5	-	-	-	-	-	-	-	-
Musculoskeletal pain	2-5	2-5	-	-	-	-	-	-	-	-
Myalgia	3-8	3-8	4	5/4	2-3/3	3	-	2	3-13	4
Myopathy	<2	<2	✔	✔	-	✔	-	✔	✔	✔
Myositis	<2	<2	-	-	-	-	✔	-	-	-
Myasthenia	<2	<2	-	-	-	-	-	<1	-	-
Neck pain	<2	<2	-	-	-	-	-	-	-	-
Neck rigidity	<2	<2	-	-	-	-	-	-	-	-
Pain in extremities	-	-	2	-	-	-	-	-	-	-
Polymyalgia rheumatica	✔	✔	✔	✔	✔	✔	✔	✔	-	✔
Rhabdomyolysis	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Shoulder pain	-	-	-	-	<1‡	-	-	-	-	-
Tendinous contracture	<2	<2	-	-	-	-	-	-	-	-
Weakness	1-2	-	-	-	-	-	-	<1	-	-
Respiratory										
Bronchitis	-	-	✔	2/3	-	-	-	-	-	7
Cough	-	-	2	-	-	-	-	3	-	-
Dyspnea	1-2	-	✔	✔	✔	✔	✔	2	-	✔
Epistaxis	<2	<2	-	-	-	-	-	-	-	-
Nasopharyngitis	4-13	4-13	4	-	-	-	-	-	-	-
Pharyngolaryngeal pain	2-5	2-5	-	-	-	-	-	-	-	-
Pulmonary edema	15	-	-	-	-	-	-	-	-	-

Adverse Events	Amlodipine/ Atorvastatin	Atorvastatin	Ezetimibe/ Simvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Niacin/ Lovastatin	Niacin/ Simvastatin	Pravastatin	Rosuvastatin	Simvastatin
Rhinitis	-	-	-	-	-	✔	5	<1	-	-
Sinusitis	-	-	✔	3/4	4†	-	-	-	-	2
Upper respiratory infection	-	-	4	-	-	-	2	1	-	-
Other										
Accidental injury	-	-	-	5/4	6†	-	-	-	-	-
Allergic reaction	-	-	-	2/1	-	-	-	<1	-	-
Amblyopia	-	-	-	-	-	✔	✔	-	-	-
Anaphylaxis	✔	✔	✔	✔	✔	✔	✔	✔	-	✔
Angioedema	-	-	✔	✔	✔	✔	✔	✔	✔	✔
Angioneurotic edema	✔	✔	-	-	-	-	-	-	-	-
Blurred vision	<2	<2	-	-	<1‡	✔	-	-	-	-
Breast enlargement	<2	<2	-	-	-	-	-	-	-	-
Cataracts	✔	✔	-	✔	✔	-	✔	✔	-	-
Cholecystitis	-	-	✔	-	-	-	-	-	-	-
Cholelithiasis	-	-	✔	-	-	-	-	-	-	-
Cystoid macular edema	-	-	-	-	-	✔	-	-	-	-
Edema	-	-	✔	-	-	✔	✔	-	-	3
Eye irritation	-	-	-	-	<1‡	✔	-	-	-	-
Facial edema	-	-	-	-	-	✔	✔	<1	-	-
Flu syndrome	-	-	-	5/7	5†	6	-	-	-	-
Gynecomastia	<1	✔	-	✔	✔	✔	-	✔	-	-
Extraocular muscle movement impaired	✔	✔	-	✔	-	-	-	✔	-	-
Infection	-	-	-	-	11†	20	-	-	-	-
Influenza	-	-	-	-	-	-	-	2	-	-
Joint swelling	<2	<2	-	-	-	-	-	-	-	-
Laryngismus	-	-	-	-	-	✔	✔	-	-	-
Larynx edema	-	-	-	-	-	✔	✔	-	-	-
Lens opacity	-	-	-	-	-	-	-	<1	-	-
Leukocytoclastic vasculitis	<1	-	-	-	-	-	-	-	-	-
Lupus erythematosus-like syndrome	✔	✔	✔	✔	✔	✔	✔	✔	-	✔
Nonthrombocytopenic purpura	<1	-	-	-	-	-	-	-	-	-
Ophthalmoplegia	✔	✔	-	✔	✔	✔	-	✔	-	-
Pain	-	-	-	-	3†	8	-	-	-	-
Parosmia	<2	<2	-	-	-	-	-	-	-	-

Adverse Events	Amlodipine/ Atorvastatin	Atorvastatin	Ezetimibe/ Simvastatin	Fluvastatin (IR/ER)	Lovastatin (IR/ER)	Niacin/ Lovastatin	Niacin/ Simvastatin	Pravastatin	Rosuvastatin	Simvastatin
Peripheral ischemia	<1	-	-	-	-	-	-	-	-	-
Petechiae	<2	<2	-	-	-	-	-	-	-	-
Photosensitivity	<2	<2	✔	✔	✔	✔	✔	✔	-	✔
Purpura	<1	-	✔	✔	✔	✔	✔	✔	-	✔
Taste loss	<2	<2	-	-	-	-	-	-	-	-
Taste disturbance	<2	<2	-	✔	-	-	-	<1	-	-
Tendinous contracture	<2	<2	-	-	-	-	-	-	-	-
Tendon rupture	<2	<2	-	-	-	-	✔	-	-	-
Tinnitus	<1	<2	-	-	-	-	-	-	-	-
Tongue edema	-	-	-	-	-	✔	✔	-	-	-
Vasculitis	✔	✔	✔	✔	✔	✔	✔	✔	-	✔
Visual disturbance	-	-	-	-	✔	-	-	2	-	-
Weight loss	<1	-	-	-	-	-	-	-	-	-
Xerophthalmia	<1	-	-	-	-	-	-	-	-	-

✔ Percent not specified
- Event not reported
†Extended-release formulation
‡Immediate-release formulation

VII. Dosing and Administration

The usual dosing regimens for the HMG-CoA reductase inhibitors are listed in Table 8. All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin immediate-release products, which should be divided into twice-daily dosing. Atorvastatin, rosuvastatin and fluvastatin extended-release formulation are the only statins that may be administered at any time in the day. The other statins should be administered in the evening or at bedtime to target the time of maximum cholesterol synthesis.

Table 8. Usual Dosing Regimens for the HMG-CoA Reductase Inhibitors[1-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine and atorvastatin	Coronary Artery Disease: Amlodipine: 5-10 mg once daily Dysbetalipoproteinemia, Hypertriglyceridemia and Primary/Secondary Prevention of Cardiovascular Disease: 10-80 mg once daily Homozygous Familial Hypercholesterolemia: Atorvastatin 10-80 mg daily Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb): Atorvastatin: initial, 10-20 mg once daily. For LDL-C reduction >45%, initiate at 40 mg once daily; maximum, 80 mg daily Hypertension or Angina: Amlodipine: initial, 5 mg once daily; maximum, 10 mg daily Amlodipine/atorvastatin may be substituted for its individually titrated components. Patients may be given the equivalent dose of amlodipine/atorvastatin or a dose of amlodipine/atorvastatin with increased amounts of amlodipine, atorvastatin or both for additional antianginal effects, blood pressure lowering, or lipid lowering effect. Amlodipine/atorvastatin may be used to provide additional therapy for patients already on one of its components. As initial therapy for one indication and continuation of treatment of the other, the recommended starting dose of amlodipine/atorvastatin should be selected based on the continuation of the component being used and	Heterozygous Familial Hypercholesterolemia: 10-17 years of age: atorvastatin, 10 mg once daily; maximum, 20 mg daily Hypertension: 6-17 years of age: amlodipine, 2.5-5 mg once daily There have been no studies conducted to determine the safety or effectiveness of amlodipine/atorvastatin in pediatric populations.	Tablet: 2.5 mg/10 mg 2.5 mg/20 mg 2.5 mg/40 mg 5 mg/10 mg 5 mg/20 mg 5 mg/40 mg 5 mg/80 mg 10 mg/10 mg 10 mg/20 mg 10 mg/40 mg 10 mg/80 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	the recommended starting dose for the added monotherapy. Amlodipine/atorvastatin may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina. The recommended starting dose of amlodipine/atorvastatin should be based on the appropriate combination of recommendations for the monotherapies.		
Atorvastatin	Dysbetalipoproteinemia, Hypertriglyceridemia and Primary/Secondary Prevention of Cardiovascular Disease: 10-80 mg once daily Homozygous Familial Hypercholesterolemia: 10-80 mg once daily Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb): Initial, 10-20 mg once daily. For LDL-C reduction >45%, initiate at 40 mg once daily; maximum, 80 mg/day	Heterozygous Familial Hypercholesterolemia: 10-17 years of age: initial, 10 mg once daily; maximum, 20 mg daily Safety and efficacy in children younger than 10 years of age have not been established.	Tablet: 10 mg 20 mg 40 mg 80 mg
Ezetimibe and simvastatin	Homozygous Familial Hypercholesterolemia: 10/40 mg to 10/80 mg once daily in the evening Primary Hypercholesterolemia and Mixed Dyslipidemia: Initial, 10/20 mg once daily in the evening; 10/10 mg may be considered in patients requiring less aggressive LDL-C lowering. Patients who require a larger reduction in LDL-C (>55%) may be started at 10/40 mg once daily	The effects of ezetimibe coadministered with simvastatin compared to simvastatin monotherapy have been evaluated in adolescent boys and girls with heterozygous familial hypercholesterolemia. The patients received coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, coadministered ezetimibe and 40 mg simvastatin or 40 mg simvastatin monotherapy for the next 27 weeks, and open-label coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter. Coadministration of ezetimibe with simvastatin at doses greater than 40 mg/day has not been studied in adolescents. Ezetimibe/simvastatin has not	Tablet: 10 mg/10 mg 10 mg/20 mg 10 mg/40 mg 10 mg/80 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		been studied in patients younger than 10 years of age or in premenarchal girls.	
Fluvastatin	Atherosclerosis, Primary Hypercholesterolemia, Mixed Dyslipidemia, Secondary Prevention of Coronary Events: For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is one 40 mg capsule in the evening, one 80 mg extended-release tablet administered once daily at any time of the day, or one 40 mg capsule given twice daily. For patients requiring LDL-C reduction to a goal of <25%, a starting dose of 20 mg may be used.	Heterozygous Familial Hypercholesterolemia: 10-16 years of age: initial: 20 mg capsule once daily in the evening; maintenance, 20-80 mg daily as either two 40 mg capsules in divided doses or one extended-release tablet daily; maximum, 80 mg Safety and efficacy in children younger than 10 years of age have not been established.	Capsule: 20 mg 40 mg Tablet (ER): 80 mg
Lovastatin	Coronary Heart Disease and Primary Prevention of Cardiovascular Disease: Tablet: initial, 20 mg once daily with the evening meal; maintenance 10-80 mg/day given once or twice daily; maximum, 80 mg/day Extended-release tablet: 20-60 mg once daily in the evening Primary Hypercholesterolemia and Mixed Dyslipidemia: Tablet: initial, 20 mg once daily with the evening meal; maintenance 10-80 mg/day given once or twice daily; maximum, 80 mg/day Extended-release tablet: 20-60 mg once daily in the evening	Heterozygous Familial Hypercholesterolemia: 10-17 years of age: tablet, 10-40 mg once daily with the evening meal; maximum, 40 mg/day Safety and efficacy in children have not been established with the extended-release tablet.	Tablet: 10 mg 20 mg 40 mg Tablet (ER): 20 mg 40 mg 60 mg
Niacin and lovastatin	Primary Hypercholesterolemia, Mixed Dyslipidemia, Hypertriglyceridemia, and Primary/Secondary Prevention of Cardiovascular Disease: Initial dose: 500 mg/20 mg once daily at bedtime. The dose of niacin extended-release should not be increased by more than 500 mg every 4 weeks. Maintenance dose: 1,000 mg/20 mg to 2,000 mg/40 mg once daily; maximum, 2,000 mg/40 mg daily	Safety and efficacy in children have not been established	Tablet: 500 mg/20 mg 750 mg/20 mg 1,000 mg/20 mg 1,000 mg/40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Patients already receiving a stable dose of niacin extended-release tablets may be switched directly to a niacin-equivalent dose of niacin extended-release/lovastatin tablets. Patients previously receiving niacin products other than niacin extended-release tablets should be started on niacin extended-release tablets with the recommended niacin extended-release tablets titration schedule, and the dose should subsequently be individualized. Patients already receiving a stable dose of lovastatin may receive concomitant dosage titration with niacin extended-release tablets, and switch to niacin extended-release/lovastatin tablets once a stable dose of niacin extended-release tablets has been reached.		
Niacin and simvastatin	Primary Hypercholesterolemia, Mixed Dyslipidemia, and Hypertriglyceridemia: Initial: 500/20 mg once daily at bedtime for patients not taking niacin extended-release and patients taking niacin products other than niacin extended-release. The dose of niacin extended-release should not be increased by more than 500 mg every 4 weeks. Maintenance dose: 1,000 mg/20 mg to 2,000 mg/40 mg once daily; maximum, 2,000 mg/40 mg daily, depending on patient tolerability and lipid levels If niacin/simvastatin therapy is discontinued for an extended period of time (more than 7 days), re-titration as tolerated is recommended.	Safety and efficacy in children have not been established	Tablet: 500 mg/20 mg 750 mg/20 mg 1000 mg/20 mg
Pravastatin	Primary Hypercholesterolemia, Mixed Dyslipidemia, Dysbetalipoproteinemia, Hypertriglyceridemia, and Primary/Secondary Prevention of Cardiovascular Disease: Initial, 40 mg once daily; maximum 80 mg once daily	Heterozygous Familial Hypercholesterolemia: 8-13 years of age: 20 mg once daily at bedtime 14-18 years of age: 40 mg once daily at bedtime	Tablet: 10 mg 20 mg 40 mg 80 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Rosuvastatin	Atherosclerosis, Dysbetalipoproteinemia, Primary Hypercholesterolemia, Mixed Dyslipidemia, Hypertriglyceridemia, and Secondary Prevention of Cardiovascular Disease: Initial: 10-20 mg once daily; maximum, 40 mg once daily. The 40 mg dose should be reserved for patients who failed therapy with the 20 mg dose Homozygous Familial Hypercholesterolemia: Initial, 20 mg once daily; maximum, 40 mg daily	Heterozygous Familial Hypercholesterolemia: 10-17 years of age: 5-20 mg once daily	Tablet: 5 mg 10 mg 20 mg 40 mg
Simvastatin	Dysbetalipoproteinemia, Primary Hypercholesterolemia, Mixed Dyslipidemia, Hypertriglyceridemia, and Prevention of Cardiovascular Disease: Initial, 20-40 mg once daily in the evening; dose range, 5-80 mg daily. For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Homozygous Familial Hypercholesterolemia: 40 mg once daily in the evening or 80 mg daily in 3 divided doses (20 mg, 20 mg, and 40 mg in the evening)	Heterozygous Familial Hypercholesterolemia: 10-17 years of age: 10 mg once daily in the evening; maximum, 40 mg/day	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg

ER=extended-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the HMG-CoA reductase inhibitors are summarized in Table 9.

Table 9. Comparative Clinical Trials with the HMG-CoA Reductase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Familial Hypercholesterolemia (FH)				
Rodenburg et al.[34] (2007) Pravastatin 20 mg (children <14 years of age) or pravastatin 40 mg (children ≥14 years of age)	FU Children diagnosed with FH, between 8 and 18 years of age, on a fat-restricted diet ≥3 months, with LDL-C ≥4.0 mmol/L and triglyceride levels <4.0 mmol/L on 2 different occasions, using adequate contraception, not on any treatment for hypercholesterolemia, including plant sterol or stanol products	N=214 2 years (mean duration of total treatment with a statin was 4.5 years)	Primary: Percentage change in TC, LDL-C, TG, HDL-C, predictors of smaller carotid IMT, and safety	Primary: Statin therapy was associated with a 22.5% reduction in TC from baseline. Statin therapy was associated with a 29.2% reduction in LDL-C from baseline. Statin therapy was associated with a 3.1% increase in HDL-C from baseline. Statin therapy was associated with a 1.9% reduction in TG from baseline. The study found several independent predictors of smaller carotid IMT: IMT at statin initiation (P<0.001), age at statin initiation (P=0.016), male sex (P<0.001), and the duration of statin therapy (P<0.001).
Avis et al.[35] (2007) Standard statin therapy (pravastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, atorvastatin) vs placebo	MA Randomized, placebo-controlled trials, evaluating statin therapy in patients, aged <18 years, with heterozygous FH	N=798 (6 trials) Up to 2 years	Primary: Percentage change in TC, LDL-C, TG, HDL-C, apo B, apo AI, the difference in absolute changes in IMT, and safety	Primary: Statin therapy was associated with a 23% reduction in TC compared with placebo (95% CI, 19 to 27). Statin therapy was associated with a 30% reduction in LDL-C compared with placebo (95% CI, 24 to 36). Statin therapy was associated with a 3.6% increase in HDL-C compared with placebo (95% CI, 1.33 to 5.94). Statin therapy was associated with a 25% reduction in apo B compared with placebo (95% CI, 19 to 31). Statin therapy was associated with a 2.4% reduction in apo AI compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				with placebo (95% CI, 0.41 to 4.45). Statin therapy was associated with a significant carotid IMT regression compared with placebo (P=0.02). Statin therapy was not associated with a significant risk of adverse events compared with placebo (RR, 0.99; 95% CI, 0.79 to 1.25). Statin therapy was not associated with a significant risk of AST (RR, 0.98; 95% CI, 0.23 to 4.26), ALT (RR, 2.03; 95% CI, 0.24 to 16.95), or CK elevation (RR, 1.38; 95% CI, 0.18 to 10.82) compared with placebo.
Shafiq et al.[36] (2007) Statins (lovastatin, pravastatin, simvastatin, atorvastatin vs placebo	MA Randomized, double-blind, controlled trials comparing statins with placebo in pediatric and adolescent patients with FH	N=798 (6 trials) 12-104 weeks	Primary Percent change in LDL-C, TC, TG, HDL-C	Primary Statin therapy was associated with a significant reduction in LDL-C compared with placebo. Statin therapy was associated with a significant reduction in TC compared with placebo. Statin therapy was associated with a significant reduction in TG compared with placebo. Statin therapy was associated with a significant increase in HDL-C compared with placebo.
Marais et al.[37] (2008) Rosuvastatin 80 mg once daily for 6 weeks, following an 18-week open label titration phase during which patients received rosuvastatin 20 mg once daily for 6 weeks, titrated up to 40 mg/day for 6	RCT, DB, XO Patients >10 years of age, weighing ≥32 kg, with homozygous FH, fasting LDL-C >500 mg/dL, TG <600 mg/dL, and either xanthomata before 10 years of age or both parents with FH	N=44 24 weeks	Primary Percent change in LDL-C from baseline to week 18 Secondary Response rate, percent change in TC, apo B, TG, HDL-C	Primary Patients receiving rosuvastatin 20-80 mg experienced a significant reduction in LDL-C from baseline after 18 weeks of therapy (21.4%; P<0.0001). Patients without a portacaval shunt and those not receiving plasmaphoresis who were treated with rosuvastatin 20-80 mg experienced a 15% reduction in LDL-C from baseline after 18 weeks of therapy. Secondary: Rosuvastatin treatment was associated with an overall 72% response rate, defined as ≥15% reduction in baseline LDL-C. Patients receiving rosuvastatin 20-80 mg experienced a significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks, titrated up to 80 mg/day for another 6 weeks, after a 4-week dietary lead-in period vs atorvastatin 80 mg once daily for 6 weeks, following an 18-week open label titration phase during which patients received rosuvastatin 20 mg once daily for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, after a 4-week dietary lead-in period				reduction in TC and apo B from baseline after 18 weeks of therapy (20%; P<0.0001). Patients receiving rosuvastatin 20-80 mg experienced a non-significant increase in TG and HDL-C from baseline after 18 weeks of therapy (3.3% and 3.1%, respectively; P>0.05). At week 24, patients randomized to rosuvastatin and atorvastatin did not differ in the magnitude of LDL-C reduction from baseline (19.1% vs 18%; P=0.67). At week 24, there was no statistically significant difference between patients randomized to rosuvastatin and atorvastatin in reductions from baseline in TC (17.6% vs 17.9%; P=0.91), TG (6.3% vs 13.9%; P=0.21), or apo B (11.4% vs 11.7%; P=0.90). The only statistically significant difference between the two groups was in apo AI change from baseline. While patients receiving rosuvastatin experienced an increase, atorvastatin-treated patients exhibited a reduction in apo AI (P=0.001).
Arca et al.[38] (2007) Atorvastatin 10 mg daily, titrated to LDL-C goal, up to 80 mg daily for 24 weeks, following a 6-week dietary lead-in period	OL, R Patients between 30 and 75 years old with diagnosis of familial combined hyper-lipidemia with TC and/or triglyceride levels ≥90th Italian population percentiles, and/or	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A, endothelin-1	Primary: At 24 weeks, a greater percentage of patients on atorvastatin therapy was able to reach recommended lipid targets, compared to patients randomized to fenofibrate therapy (P=0.02). Atorvastatin therapy was associated with a significant 9% reduction in TC compared with fenofibrate therapy (95% CI, 3% to 15.1%; P=0.004). Atorvastatin therapy was associated with a significant 17% reduction in LDL-C compared with fenofibrate therapy (95% CI, 8% to 26.1%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fenofibrate 200 mg daily for 24 weeks, following a 6-week dietary lead-in period	hyperapobetalipo-proteinemia; patients were excluded if they had type III hyperlipidemia, were obese, had uncontrolled diabetes mellitus, or were taking lipid-lowering drugs			Fenofibrate therapy was associated with a significant 15.5% reduction in TG compared with atorvastatin therapy (95% CI, 3.35% to 27.7%; P=0.013). Fenofibrate therapy was associated with a significant 14.2% increase in HDL-C compared with atorvastatin therapy (95% CI, 3.8% to 24.6%; P=0.008). Fenofibrate therapy was associated with a significant 5.2% and 22% increase in apo AI and apo AII compared with atorvastatin therapy (P=0.044 and P<0.001, respectively). Fenofibrate therapy was associated with a significant 16.7% reduction in endothelin-1 from baseline (P<0.05). Atorvastatin was not associated with a significant change in endothelin-1.
Gagné et al.[162] (2002) Statin 40 mg for up to 14 weeks, followed by the addition of ezetimibe 10 mg daily for another 12 weeks, separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily and addition of ezetimibe 10 mg daily for another 12	DB, MC, RCT Patients ≥12 years old (or with body weight ≥40 kg) with HoFH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day)	N=50 26 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (20.7% vs 6.7%; P=0.007). Secondary: Total cholesterol was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (18.7% vs 5.3%; P<0.01). There was no statistically significant difference in any of the other secondary outcome measures between the two groups (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks, separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily Statins used in the study included simvastatin and atorvastatin.				
Primary Hypercholesterolemia				
Preston et al.[143] (2007) RESPOND Atorvastatin-amlodipine 5 mg/10 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/10 mg once daily, separate entities vs atorvastatin-	DB, RCT Patients 18-75 years of age with hypertension (HTN) and dyslipidemia	N=1,660 8 weeks	Primary: Mean change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and reduction of LDL-C Secondary: Augmentation of blood pressure-lowering with the addition of atorvastatin and augmentation of LDL-C-lowering with the addition of amlodipine, reduction in the Framingham risk	Primary: Regardless of dose, combination therapy with atorvastatin and amlodipine was associated with greater reduction in SBP from baseline compared to atorvastatin alone (P<0.001). Regardless of dose, combination therapy with atorvastatin and amlodipine was associated with greater reduction in LDL-C from baseline compared to amlodipine alone (P<0.001). Secondary: Regardless of dose, there was no significant difference in terms of SBP-lowering from baseline between patients taking atorvastatin and amlodipine and those on amlodipine monotherapy (P>0.05). Regardless of dose, there was no significant difference in terms of LDL-C-lowering from baseline between patients taking atorvastatin and amlodipine and those on atorvastatin monotherapy (P>0.05). Atorvastatin-amlodipine 5/10 mg once daily was more effective in reducing baseline LDL-C level compared to atorvastatin monotherapy (P=0.007). A maximal reduction in the Framingham risk scores was observed in the atorvastatin-amlodipine 5/80 mg and atorvastatin-amlodipine 10/80 mg

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5 mg/20 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/20 mg once daily, separate entities vs atorvastatin-amlodipine 5 mg/40 mg once daily, separate entities vs atorvastatin-amlodipine 10 mg/40 mg once daily, separate entities vs atorvastatin-amlodipine 5 mg/80 mg once daily, separate entities			scores, adverse effects	treatment groups. The proportion of patients who discontinued therapy due to adverse effects was similar in the combination, amlodipine, and atorvastatin groups (5.6% vs 5.4% vs 4.1, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atorvastatin-amlodipine 10 mg/80 mg once daily, separate entities vs amlodipine 5 mg or 10 mg once daily vs atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg once daily vs placebo				
Flack et al.[144] (2008) CAPABLE Atorvastatin-amlodipine 5 mg/10 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/20 mg daily,	MC, OL African-Americans 18-80 years of age with uncontrolled HTN and dyslipidemia	N=489 20 weeks	Primary: Proportion of patients in 3 cardiovascular risk groups (group 1: patients without additional risk factors; group 2: patients with >1 additional risk factors, excluding CHD and diabetes; group 3: patients with CHD or CHD risk equivalent)	Primary: More patients in groups 1 and 2 had reached both their JNC 7 and NCEP ATP III goals at end point compared to the group-3 patients (69.7%, 66.7%, and 28.2%, respectively). Secondary: Atorvastatin-amlodipine therapy was associated with a 17.5 mm Hg and 10.1 mm Hg decrease in the SBP and DBP from baseline, respectively. Atorvastatin-amlodipine therapy was associated with a 23.6% reduction in LDL-C from baseline. Atorvastatin-amlodipine therapy was associated with a 17% reduction in total cholesterol from baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination entity vs atorvastatin-amlodipine 5 mg/40 mg daily, combination entity vs atorvastatin-amlodipine 5 mg/80 mg daily, combination entity vs atorvastatin-amlodipine 10 mg/10 mg daily, combination entity vs atorvastatin-amlodipine 10 mg/20 mg daily, separate entities vs atorvastatin-amlodipine 10 mg/40 mg daily, combination entity vs			who reached both their JNC 7 and NCEP ATP III goals at end point Secondary: Change from baseline in SBP and DBP, LDL-C, total cholesterol, triglycerides, HDL-C, apolipoprotein B	Atorvastatin-amlodipine therapy was associated with a 2.2% increase in HDL-C from baseline. Atorvastatin-amlodipine therapy was associated with a 6.9% reduction in TG from baseline. Atorvastatin-amlodipine therapy was associated with a 19.3% reduction in apo B from baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atorvastatin-amlodipine 10 mg/80 mg daily, combination entity				
Messerli et al.[145] (2006) AVALON Amlodipine 5 mg daily for 8 weeks, followed by the addition of atorvastatin 10 mg for another 8 weeks, followed by a 12-week open-label treatment vs atorvastatin 10 mg daily for 8 weeks, followed by the addition of amlodipine 5 mg for another 8 weeks, followed by a 12-week open-label treatment vs atorvastatin-amlodipine 5 mg/10 mg daily for 16 weeks,	DD, MC, OL, RCT Patients with hypertension and dyslipidemia	N=847 28 weeks	Primary: Proportion of patients who reached both their JNC 7 and NCEP ATP III goals, side effects	Primary: More patients in the combination group reached both their JNC 7 and NCEP ATP III LDL-C goals at 8 weeks compared to patients receiving amlodipine or atorvastatin as monotherapy (45%, 8.3%, and 28.6%, respectively; P<0.001). The incidence of side effects was similar across all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by a 12-week open-label treatment vs placebo daily for 16 weeks, followed by a 12-week open-label treatment				
Piorkowski et al.[62] (2007) Atorvastatin 40 mg once daily vs atorvastatin 10 mg once daily in addition to ezetimibe 10 mg daily, separate entities	RCT Patients between 18 and 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10-20 mg daily, receiving aspirin and clopidogrel	N=56 4 weeks	Primary: Change in liver transaminases, CK, HDL, LDL, and TG from baseline, percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L)	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL in either group. Both groups exhibited a statistically significant reduction in LDL-C from baseline (P<0.005). There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline. Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in triglyceride level from baseline (P<0.005 and P<0.05, respectively). There was no statistically significant difference between the two groups in the percentage of patients achieving the ATP III LDL-C goal (≤2.5 mmol/L).
Constance et al.[63] (2007) Atorvastatin 20 mg daily for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, A1C ≤10%, ALT/AST levels <1.5 times the ULN, CK <1.5 times the ULN	N=661 6 weeks	Primary: Change from baseline in LDL-C at 6 weeks Secondary: Change from baseline in TC, HDL-C, TG, non–HDL-C, apo B,	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin 20 mg monotherapy group (P≤0.001). Secondary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant reduction from baseline in TC, non-HDL, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe 10 mg daily added to simvastatin 20 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities, for 6 weeks, following a 4-week atorvastatin 10 mg run-in period			LDL-C:HDL-C ratio, and TC:HDL-C ratio	compared with the atorvastatin 20 mg monotherapy group (P≤0.001). Patients on the ezetimibe/simvastatin 10/40 mg combination therapy experienced a statistically significant reduction in CRP from baseline compared with the atorvastatin 20 mg monotherapy group (P=0.006). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy achieved LDL-C <2.5 mmol/L, compared to the atorvastatin 20 mg group (90.5%, 87%, and 70.4%, respectively; P≤0.001). The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy and atorvastatin monotherapy groups (0.5%, 0.5%, and 2.3%, respectively).
Pearson et al.[64] (2007) Atorvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 6 weeks vs simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 12 weeks vs ezetimibe 10 mg	MA Three identical, prospective 12-week studies randomizing patients to placebo, ezetimibe, ezetimibe with simvastatin or simvastatin alone, and one phase III double-blind, active-controlled study allocating patients to ezetimibe/simvastatin or atorvastatin for 6 weeks	N=4,373 (4 trials) up to 12 weeks	Primary: Change from baseline in LDL-C level, CRP, proportion of patients reaching LDL-C target (<100 mg/dL or <70 mg/dL)	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (52.5% vs 38%; P<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the atorvastatin monotherapy group (53.4% vs 45.3%; P<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant CRP reduction from baseline compared with the simvastatin monotherapy group (31% vs 14.3%; P<0.001). Patients on the ezetimibe/simvastatin combination therapy experienced a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 12 weeks vs ezetimibe 10 mg daily added to simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily, separate entities, for up to 12 weeks vs placebo for 12 weeks				similar CRP reduction from baseline compared with the atorvastatin monotherapy group (25.1% vs 24.8%). The reduction in CRP from baseline was not significantly different between simvastatin 10 mg and placebo groups (P>0.10). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (78.9% vs 43.1%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (37% vs 5.7%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the atorvastatin group (79.8% vs 61.9%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the atorvastatin group (36.2% vs 16.8%; P<0.001).
Goldberg et al.[65] (2006) VYTAL Atorvastatin 10 mg daily vs atorvastatin 20 mg daily vs atorvastatin 40 mg	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with A1C ≤8.5%, LDL-C >100 mg/dL and a triglyceride level <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week 6 Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dl, percent	Primary: Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 10 mg or 20 mg daily (53.6%, 38.3%, and 44.6%, respectively; P<0.001). Patients randomized to simvastatin 40 mg/ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week 6 of the study compared to patients receiving atorvastatin 40 mg daily (57.6% and 50.9%, respectively; P<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (59.7%, 21.5%, and 35%, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily, separate entities			change from baseline in HDL-C, non–HDL-C, TC, TG, and CRP	A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<70 mg/dL compared to patients receiving atorvastatin 40 mg daily (74.4% and 55.2%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 20 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 10 mg or 20 mg daily (90.3%, 70%, and 82.1%, respectively; P=0.007). A greater proportion of patients randomized to simvastatin 40 mg/ezetimibe 10 mg therapy achieved LDL-C<100 mg/dL compared to patients receiving atorvastatin 40 mg daily (93.4% and 88.8%, respectively; P=0.07). Patients randomized to simvastatin/ezetimibe combination therapy, at all doses, experienced a significant increase in HDL level (P≤0.001), a greater reduction in TC, and non–HDL-C (P<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg/ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and triglyceride level compared to patients receiving atorvastatin (P=0.02). Side effects were similar in the simvastatin/ezetimibe and atorvastatin groups (19.85 vs 22.7%).
Rodney et al.[148] (2006) Ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 12 weeks vs	DB, MC, PG, RCT African-American patients with LDL-C ≥145 mg/dL but ≤250 mg/dL, TG ≤350 mg/dL	N=247 12 weeks	Primary: Mean change from baseline in LDL-C level, total cholesterol, TG, HDL-C, non–HDL-C, apo B	Primary: Patients on the combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the simvastatin monotherapy group (45.6% vs 28.3%; P≤0.01). Patients on the combination therapy experienced a statistically significant reduction in total cholesterol from baseline compared to the simvastatin monotherapy group (33% vs 21%; P≤0.01). Patients on the combination therapy experienced a statistically significant triglyceride reduction from baseline compared to the simvastatin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 20 mg, in addition to placebo, separate entities, for 12 weeks				monotherapy group (22% vs 15%; P≤0.01). Patients on the combination therapy experienced a statistically significant non–HDL-C reduction from baseline compared to the simvastatin monotherapy group (42% vs 26%; P≤0.01). Patients on the combination therapy experienced a statistically significant apo B reduction from baseline compared to the simvastatin monotherapy group (38% vs 25%; P≤0.01). There was no difference in the change of HDL level from baseline between the two groups (~1-2% increase in each group). There was no statistically significant difference in side effects between the combination therapy and simvastatin groups.
Masana et al.[149] (2005) Ezetimibe 10 mg daily, in addition to simvastatin 10 mg titrated up to 80 mg daily, separate entities vs simvastatin 10 mg titrated up to 80 mg daily, in addition to placebo, separate entities	DB, ES, MC, RCT Patients with primary hypercholesterolemia ≥18 years of age, currently taking a stable daily dose of a statin ≥6 weeks, with LDL-C above the NCEP ATP II guideline target level, TG <350 mg/dL	N=355 48 weeks	Primary: Percent change from baseline in LDL-C between the study groups at week 12 Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, non–HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C at 12 weeks	Primary: At week 12, simvastatin-ezetimibe groups experienced a statistically significant 27% reduction in LDL-C compared to patients on simvastatin monotherapy (P<0.001). The benefit was maintained up to week 48 of the study. Secondary: At week 12, simvastatin-ezetimibe groups experienced a statistically significant reduction in total cholesterol, TG, non–HDL-C, ratios of LDL-C:HDL-C, and TC:HDL-C, compared to patients on simvastatin monotherapy (P<0.001). At week 12, simvastatin-ezetimibe groups experienced a non-significant 2.6% increase in HDL-C compared to patients on simvastatin monotherapy (P=0.07). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe groups (17% and 19%, respectively). There were no cases of rhabdomyolysis or myopathy during the study.
Denke et al.[150] (2006)	DB, MC, PG, RCT	N=3,030	Primary: Mean change from	Primary: The addition of ezetimibe to ongoing statin therapy, as compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
EASE Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a cholesterol-lowering diet	6 weeks	baseline in LDL-C level, proportion of patients who reached LDL-C target, change in serum cholesterol, TG, HDL in patients with diabetes, metabolic syndrome or neither	addition of placebo to ongoing statin therapy, was associated with an additional LDL-C reduction of 24.8% (diabetic patients), 21.4% (metabolic syndrome patients), and 22.4% (neither) from baseline (P<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional triglyceride reduction of 12.3% (diabetic patients), 10.7% (metabolic syndrome patients), and 11% (neither) from baseline (P<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional increase in HDL cholesterol among diabetic patients (P<0.001) and patients with metabolic syndrome (P=0.002) from baseline. The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional non-HDL cholesterol reduction of 21.8% (diabetic patients), 19.5% (metabolic syndrome patients), and 20.3% (neither) from baseline (P<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction in total cholesterol of 16% (diabetic patients), 14.8% (metabolic syndrome patients), and 15% (neither) from baseline (P<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction in apo B to apo AI ratio of 17.7% (diabetic patients), 16.6% (metabolic syndrome patients), and 15.1% (neither) from baseline (P<0.001). The addition of ezetimibe to ongoing statin therapy, as compared to the addition of placebo to ongoing statin therapy, was associated with an additional reduction from baseline in CRP of 14.8% and 9.7% among

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				diabetic patients (P<0.001) and patients with metabolic syndrome (P=0.027), respectively. A significantly greater proportion of patients randomized to the ezetimibe combination therapy achieved their NCEP-ATP LDL-C goals compared to the control group (P<0.001). Side effects were similar across all treatment groups.
Pearson et al.[151] (2005) EASE Ezetimibe 10 mg, in addition to ongoing statin therapy for 6 weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	DB, MC, PG, RCT Subanalysis of the EASE study; patients >65 years old with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a cholesterol-lowering diet	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target across different races and ethnicities, change in serum cholesterol, TG, HDL at 6 weeks	Primary: Compared to placebo, patients on the ezetimibe combination therapy experienced an LDL-C reduction of 23% (white patients), 23% (African American patients), and 21% (Hispanic patients) from baseline (P<0.001). The difference in LDL-C lowering among the three races studied was not statistically significant (P>0.5). A significantly greater proportion of patients randomized to the ezetimibe combination therapy achieved their NCEP ATP LDL-C goal compared to the control group (P<0.001). Patients on the ezetimibe combination therapy experienced a total cholesterol reduction of 15.3 mg/dL from baseline compared to the control group (P<0.001). Patients on the ezetimibe combination therapy experienced a triglyceride reduction of 11.5 mg/dL from baseline compared to the control group (P<0.001). Patients on the ezetimibe combination therapy experienced an increase in HDL of 2.1 mg/dL from baseline when compared to the control group (P<0.001). Side effects were similar across treatment groups and races.
Sampalis et al.[152] (2007) Ezetimibe 10 mg, in addition to ongoing statin therapy for 6	SA Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP	N=825 6 weeks	Primary: Reduction in the 10-year risk of CAD after 6 weeks	Primary: The addition of ezetimibe to ongoing statin therapy was associated with a 25.3% reduction in the 10-year risk of CAD (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks, separate entities vs placebo, in addition to ongoing statin therapy for 6 weeks, separate entities	ATP goals on statin therapy			
Robinson et al.[176] (2009) VYMET Ezetimibe-simvastatin 10/20 mg to 10/40 mg once daily vs atorvastatin 10-40 mg once daily	RCT, DB, MC, PG Patients 18 to 79 years of age with metabolic syndrome and hypercholesterolemia who were at moderately high or high risk for coronary heart disease	N=1,128 6 weeks	Primary: Percentage of change from baseline in LDL-C Secondary: Changes in other lipids, lipoprotein ratios, high-sensitivity C-reactive protein, and attainment of prespecified lipid levels	Primary: After 6 weeks, the percent change in LDL-C was significantly greater with ezetimibe/simvastatin than with atorvastatin (all dose comparisons, P<0.001). Secondary: The percent of patients who achieved LDL-C <70 mg/dl and the non-HDL-C goal was significantly greater for ezetimibe/simvastatin than for atorvastatin (all dose comparisons, P<0.05). Treatment with ezetimibe/simvastatin led to a significantly greater reduction in TC, non-HDL-C, apo B, and all 4 lipid ratios compared to atorvastatin (all dose comparison, P<0.001). HDL-C cholesterol increased to a greater extent with ezetimibe/simvastatin 10/20 mg compared to atorvastatin 10 mg (P<0.05) and ezetimibe/simvastatin 10/40 mg compared to atorvastatin 40 mg (P<0.01). Changes in triglycerides, VLDL-C, apolipoprotein A-I, and high-sensitivity C-reactive protein were comparable for both treatments, except that apolipoprotein A-I was significantly increased with ezetimibe/simvastatin 10/20 mg versus atorvastatin 10 mg (P<0.05). The rates of adverse events were similar for both treatments.
Farnier et al.[189] (2009)	RCT, DB, AC, MC, PG	N=618 6 weeks	Primary: Mean percent change in LDL-C	Primary: Treatment with EZE/SIMVA led to a -27.7% reduction in LDL-C from baseline (P≤0.001) and rosuvastatin led to a -16.9% reduction in LDL-C

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe-simvastatin (EZE/SIMVA) 10/20 mg daily vs rosuvastatin 10 mg daily	Patients 18 to 80 years of age with hypercholesterolemia (LDL-C ≥100 and ≤160 mg/dl) and high cardiovascular risk who were taking a stable daily dose of one of the following statins for ≥6 weeks as monotherapy: atorvastatin (10 to 20 mg), fluvastatin (80 mg), pravastatin (40 mg), rosuvastatin (5 mg), or simvastatin (20 to 40 mg)		from baseline to study endpoint Secondary: Percentages of patients achieving LDL-C <100 mg/dl) and <70 mg/dl), mean percent change in TC, TG, HDL-C, non-HDL-C, LDL-C/HDL-C and TC/HDL-C ratios, apolipoprotein (apo) B and hs-CRP	from baseline (P≤0.001) in high-risk patients with hypercholesterolemia, despite prior use of statin monotherapy. There was a significant difference in LDL-C reduction between EZE/SIMVA and rosuvastatin (-10.7%; P≤0.001). Secondary: A greater proportion of patients in the EZE/SIMVA group achieved LDL-C goals of <100 mg/dl (72.5% vs 56.2%, respectively), <79 mg/dl (38.0% vs 18.9%, respectively) and <70 mg/dl (25.2% vs 11.1%, respectively) compared to rosuvastatin (P≤0.001 for all assessments). Treatment with EZE/SIMVA and rosuvastatin led to improvements in TC (-17.5% and -10.3%, respectively; P≤0.001), TG (-11.0% and -5.3%, respectively; P=0.056), non-HDL-C (-23.4% and -14.0%, respectively; P≤0.001), apo B (-17.9% and -9.8%, respectively; P≤0.001), LDL-C/HDL-C (-27.4% and -17.8%, respectively; P≤0.001), TC/HDL-C (-17.8% and -11.5%, respectively; P≤0.001) and HDL-C (2.1% and 3.0%, respectively; P=0.433). There was no significant difference in hs-CRP among the treatment groups (P=0.172). Adverse events (AE) were reported by 7.1% of patients in the EZE/SIMVA group and 11.2% of patients in the rosuvastatin group. There were no differences between the treatment groups in AEs.
Roeters van Lennep et al.[170] (2008) EASEGO Ezetimibe-simvastatin (EZE/SIMVA) 10/20 mg once daily vs	RCT, OL Patients >18 years of age with controlled stable type 2 diabetes mellitus (>3 months) and/or established coronary heart disease who were on a stable daily statin dose of either atorvastatin 10 mg or simvastatin 20 mg	N=367 15 weeks	Primary: Percentages of patients reaching the ESC goal LDL-C <97 mg/dl Secondary: TC, TG, HDL-C, apo-B, and TC/HDL-C	Primary: Overall, the LDL-C target of <97 mg/dl was achieved in 67% of the patients in the EZE/SIMVA group and 26% of the patients in the doubling statin group. After doubling the simvastatin dose from 20 to 40 mg, 24% of patients achieved LDL-C <97 mg/dl. After switching to EZE/SIMVA, 73% of patients reached LDL-C <97 mg/dl (P<0.0001). After doubling the atorvastatin dose from 10 to 20 mg, 28% of patients achieved LDL-C <97 mg/dl. After switching to EZE/SIMVA, 57% of patients achieved LDL-C 97 mg/dl (P<0.0004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doubling of statin dose (atorvastatin 20 mg or simvastatin 40 mg) once daily Patients were randomized to continuation of statin monotherapy at a double dose or to EZE/SIMVA	for at least 4 weeks. Entry lipid values while on statin monotherapy were: LDL-C 97 to 193 mg/dl, TG ≤354 mg/dl and TC ≤270 mg/dl			After doubling the statin dose, LDL-C <77 mg/dl was achieved in 3% of patients and in 30% of the patients receiving EZE/SIMVA. Secondary: The mean percent change in TC, TC/HDL-C and apo-B were -6.6%, -6.1% and -7.2%, respectively after doubling the statin dose compared to -17.7%, -13.5%, and -19.7%, respectively in the EZE/SIMVA group (all, P<0.001). HDL-C increased 1.0% after doubling the statin dose compared to -2.6% in the EZE/SIMVA group (P=0.02). There was no significant difference in TG among the treatment groups. There were no significant differences between the treatment groups in adverse events.
Reckless et al.[190] (2008) Ezetimibe-simvastatin (EZE/SIMVA) 10/40 mg once daily vs existing statin therapy (with the dose doubled) administered once daily	RCT, OL, MC, AC, PG Patients ≥18 years of age hospitalized for an acute coronary event and taking a stable daily dose of one of the following statin medications for ≥6 weeks: atorvastatin (10-40 mg), fluvastatin (20-40 mg), lovastatin (10-20 mg), pravastatin (10-20 mg), rosuvastatin (10-20 mg), or simvastatin (10-40 mg)	N=424 12 weeks	Primary: Absolute LDL-C value at study end point Secondary: TC, TG, HDL-C, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, apolipoprotein (apo) B, CRP, percentages of patients in each treatment group achieving LDL-C ≤100 mg/dl, <77 mg/dl and <70 mg/dl	Primary: Treatment with EZE/SIMVA lowered LDL-C by -25.5 mg/dl (27%) compared to -6.6 mg/dl (4.2%) in the statin group (P≤0.001). The absolute LDL-C value at study end point was 65.7 mg/dl in the EZE/SIMVA group and 85.8 mg/dl in the statin group. Secondary: A greater proportion of patients in the EZE/SIMVA group compared to placebo achieved LDL-C concentrations <100 mg/dl (85.8% vs 72.4%, respectively; P≤0.001), <77 mg/dl (70.1% vs 41.7%, respectively; P≤0.001) and <70 mg/dl (59.8% vs 30.7%, respectively; P≤0.001). Switching to EZE/SIMVA lowered TC by -24.0 mg/dl (14.6%) compared with -5.4 mg/dl (1.7%) in the statin group (P≤0.001). Treatment with EZE/SIMVA produced greater reductions in non- HDL-C (P≤0.001), apo B (P≤0.001), LDL-C/HDL-C (P≤0.001) and TC/HDL-C (P≤0.001) compared to the statin group. Both treatments reduced TG and CRP, and increased HDL-C to a similar extent (P≥0.160 for all). There were no significant differences in adverse events between the two treatment groups.
Alvarez-Sala et al.[184] (2008)	RCT, OL, MC, PG Patients 18 to 75	N=89 12 weeks	Primary: Percentage change in LDL-C	Primary: Fluvastatin XL + ezetimibe lowered mean LDL-C from 197 mg/dL to 97 mg/dL (-49.9%) and fluvastatin XL alone lowered mean LDL-C from 216

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluvastatin XL 80 mg once daily (nighttime) and ezetimibe 10 mg once daily vs fluvastatin XL 80 mg once daily (nighttime)	years of age with primary hypercholesterolemia (LDL-C ≥130 mg/dL and triglycerides ≤400 mg/dL)		Secondary: Percentage change in HDL-C and TG, proportions of patients achieving NCEP ATP III LDL-C goals, change in hs-CRP and other markers of inflammation, and safety	mg/dL to 135 mg/dL (-35.2%) after 12 weeks of therapy (P<0.001). Secondary: Fluvastatin XL + ezetimibe combination was associated with a significantly greater reduction from baseline in TC, TG, and apo B than fluvastatin XL alone (all, P<0.05). There was no significant change in HDL-C level with either treatment regimen. A greater proportion of patients receiving the fluvastatin XL + ezetimibe achieved NCEP ATP III LDL-C goals at week 12 compared with those receiving fluvastatin XL alone (86.5% vs 66.7%; P=0.042). There were no significant changes in levels of hs-CRP with either treatment regimen. In patients with higher baseline hs-CRP levels, the coadministration of fluvastatin XL with ezetimibe was associated with a reduced level of this inflammatory marker. Treatment with fluvastatin XL + ezetimibe or fluvastatin XL alone was associated with significant reductions in IL-1β (21%; P<0.001 and 13%; P<0.002, respectively). No significant changes were seen in levels of IL-6, TNF-α, sP-selectin, or sVCAM-1. There was no significant difference in the incidence of adverse events (AEs) between the treatment groups. Most AEs were mild or moderate in intensity, with headache being the most common (8.5%).
Stein et al.[185] (2008) Fluvastatin XL 80 mg once daily vs ezetimibe 10 mg once daily vs	RCT, DB, MC, PG Patients ≥18 years of age with dyslipidemia who had previously documented muscle related side effects (MRSEs) that had led to cessation of statin treatment or patients currently receiving statin treatment whose	N=218 12 weeks	Primary: Percent decrease in LDL-C Secondary: LDL:HDL-C, TC, TG, apolipoprotein B, proportion of patients achieving LDL-C goal	Primary: LDL-C was reduced by 15.6%, 32.8%, and 46.1% with ezetimibe monotherapy, fluvastatin XL monotherapy, and fluvastatin XL/ezetimibe combination therapy, respectively (fluvastatin XL vs ezetimibe: -17.1%, P<0.0001; fluvastatin XL/ezetimibe vs ezetimibe: -30.4%, P<0.0001). Secondary: Treatment with fluvastatin XL monotherapy and fluvastatin XL/ezetimibe combination therapy led to a greater reduction in LDL:HDL-C, TC, TG, and apolipoprotein B levels compared to ezetimibe monotherapy (all, P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluvastatin XL 80 mg and ezetimibe 10 mg once daily	quality of life was affected by MRSEs and required switching to an alternative treatment			More patients achieved their target LDL-C goal with fluvastatin XL monotherapy and fluvastatin XL/ezetimibe combination therapy compared to ezetimibe monotherapy (P<0.001 for fluvastatin XL monotherapy or combination therapy vs ezetimibe monotherapy). There were no serious adverse events, rhabdomyolysis, or creatine kinase increases ≥10 times upper limit of normal. MRSEs were reported in 24% of patients receiving ezetimibe monotherapy compared to 17% of patients in the fluvastatin XL group and 14% of patients in the fluvastatin XL/ezetimibe combination group. Differences in recurrence of MRSEs were not statistically different between treatment groups.
Lewis et al.[39] (2007) Pravastatin 80 mg once daily vs placebo	DB, MC, PC, RCT Adult patients ≥18 years of age with hypercholesterolemia, LDL-C ≥100 and TG <400 mg/dL, with at least 6-months history of compensated liver disease	N=326 36 weeks	Primary: Percent change from baseline at week 12 in LDL-C, TC, and TG, ALT event rate (ALT ≥2 times the ULN for those with normal ALT at baseline or a doubling of the baseline ALT for those with elevated ALT at baseline)	Primary: Pravastatin was associated with a statistically significant reduction in LDL-C, TC, and TG at week-12 of the study compared to placebo (P<0.0001). There was no statistically significant difference between the two study groups in the ALT event rate at any time during the study (P>0.05). By the 36th week of the study, 7.5% of patients on pravastatin and 12.5% of patients taking placebo had at least one ALT event (P=0.1379).
Sharma et al.[146] (2006) Niacin ER/lovastatin 1,500 mg/20 mg daily, combination entity, titrated up to LDL-C goal	MC, I, OL Patients with hypertension and dyslipidemia	N=131 24 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, TG, total cholesterol	Primary: Niacin ER/lovastatin therapy was associated with a statistically significant reduction from baseline in LDL-C (38%), TG (21%), and total cholesterol (25.2%) at week 24 of therapy (P<0.01). Niacin ER/lovastatin therapy was associated with a statistically significant increase from baseline in HDL-C at week 24 of therapy (18.2%; P<0.01).
Bays et al.[147] (2003) ADVOCATE	MC, OL, R Patients 18-70 years old, with 2 consecutive LDL-C	N=315 16 weeks	Primary: Percent change from baseline in LDL-C and HDL-C	Primary: Atorvastatin was associated with a statistically significant 49% reduction in LDL-C from baseline at week-16 of therapy, compared with a 39%, 42%, and 39% reduction observed with niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and simvastatin groups, respectively

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Niacin ER/lovastatin 1,000 mg/40 mg daily, combination entity vs niacin ER/lovastatin 2,000 mg/40 mg daily, combination entity vs simvastatin 40 mg daily vs atorvastatin 40 mg daily	≥160 mg/dL (if no CAD), or ≥130 mg/dL (with CAD), TG <300 mg/dL, and HDL-C <45 mg/dL (men) or <50 mg/dL (women)		Secondary: Percent change from baseline in total cholesterol, apo B, apo AI, HDL subfractions, HDL2 and HDL3 and median percent change in TG and lipoprotein(a)	(P≤0.05). Niacin ER/lovastatin 1,000/40 mg and 2,000/40 mg therapies were associated with a statistically significant increase in HDL-C from baseline at week 16 of therapy, compared with atorvastatin and simvastatin groups (17%, 32%, 6%, and 7%, respectively; P≤0.05). Secondary: Niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and atorvastatin groups experienced a statistically significant reduction in TG from baseline at week 16 of therapy, compared with the simvastatin group (29%, 49%, 31%, and 19%, respectively; P≤0.05). Niacin ER/lovastatin 1,000/40 mg and 2,000/40 mg therapies were associated with a statistically significant reduction in lipoprotein(a) from baseline at week 16 of therapy, compared with atorvastatin and simvastatin groups (19%, 21%, 0%, and 2%, respectively; P≤0.05). Niacin ER/lovastatin 1,000/40 mg, niacin ER/lovastatin 2,000/40 mg, and simvastatin groups were associated with a statistically significant increase in apo AI from baseline at week-16 of therapy, compared with the atorvastatin group (7%, 14%, 6%, and 2%, respectively; P<0.05). Niacin ER/lovastatin 2,000/40 mg and atorvastatin were associated with a statistically significant reduction in lipoprotein B from baseline at week 16 of therapy, compared with the niacin ER/lovastatin 2,000/40 and simvastatin groups (38%, 40%, 33%, and 31%, respectively; P<0.05). Niacin ER/lovastatin 1,000/40 mg, and niacin ER/lovastatin 2,000/40 mg were associated with a statistically significant increase in HDL2 and HDL3 from baseline at week 16 of therapy, compared with the atorvastatin and simvastatin groups (P<0.05).
Ballantyne et al.[164] (2008) SEACOAST I	RCT, DB, MC, AC Men and women ≥21 years of age, compliant with	N=319 24 weeks	Primary: Percent change from baseline to week 24 in non-HDL-C	Primary: Patients treated with either NER/S dose compared with those treated with simvastatin 20 mg had significant improvements in non–HDL cholesterol. Median change from baseline at week 24 in non–HDL-C was −13.9% for NER/S 1000/20 mg/day (P<0.01) and −22.5% for NER/S

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Niacin extended-release plus simvastatin (NER/S) 2000/20 mg QD vs niacin extended-release plus simvastatin (NER/S) 1000/20 mg QD vs simvastatin 20 mg QD plus niacin immediate release 50 mg QD	standard cholesterol-lowering diet for ≥4 weeks prior to screening; non-HDL cholesterol ≥130 mg/dl (CHD or CHD risk equivalent), ≥160 mg/dl (≥2 risk factors), ≥190 mg/dl (0-1 risk factors)		Secondary: Percent change from baseline to week 24 in LDL-C, HDL-C, total/HDL-C ratio, TG, Lp(a), ApoB, and ApoA-I	2000/20 mg/day (P<0.001) compared with −7.4% for simvastatin 20 mg. Secondary: Both NER/S treatment groups significantly reduced TG, Lp(a), ApoB, total/HDL-C ratio, and significantly increased HDL-C and ApoA-I/ApoB ratio compared to patients receiving simvastatin 20 mg (P<0.01, P<0.001, P<0.05). No significant difference in LDL-C was noted between the 3 treatment groups.
Ballantyne et al.[167] (2008) SEACOAST II Niacin extended-release plus simvastatin (NER/S) 2000/40 mg QD vs niacin extended-release plus simvastatin (NER/S) 1000/40 mg QD vs	RCT, DB, MC, AC Men and women ≥21 years of age, compliant with standard cholesterol-lowering diet for ≥4 weeks prior to screening; non-HDL cholesterol ≥130 mg/dl (CHD or CHD risk equivalent), ≥160 mg/dl (≥2 risk factors), ≥190 mg/dl (0-1 risk factors)	N=343 24 weeks	Primary: Percent change from baseline to week 24 in non-HDL-C. Secondary: Percent change from baseline to week 24 in LDL-C, HDL-C, total/HDL-C ratio, TG, Lp(a), ApoB, and ApoA-I.	Primary: Percent changes from baseline to week 24 in non-HDL-C in both NER/S groups were non-inferior to the simvastatin 80 mg/day group. Median changes in non-HDL-C were -10.1% for simvastatin 80 mg, -11.3% for NER/S 1000/40 mg, and -17.1% for NER/S 2000/40 mg. Secondary: Both NER/S treatment groups significantly reduced TG, Lp(a), and total/HDL-C ratio, and significantly increased HDL-C and ApoA-I levels compared to patients receiving simvastatin 80 mg (P<0.01 and P<0.001). No significant differences in LDL-C or ApoB were noted between the 3 treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 80 mg QD plus niacin IR 50 mg QD				
Karas et al.[168] (2008) OCEANS Niacin extended-release plus simvastatin (NER/S) 2000/40 mg QD	RCT, OL, PG Men and women ≥21 years of age with elevated non-HDL-C (mixed dyslipidemia); TG <500 mg/dl; LDL-C <250 mg/dl; ALT/AST <1.3 X ULN; CPK <3 x ULN; A1C <9%.	N=520 52 weeks	Primary: Evaluation of safety assessed by number, frequency, type, and severity of treatment-emergent adverse events, incidence of discontinuation due to adverse events, flushing events, and clinical laboratory results. Secondary: Median percent change from baseline for non-HDL-C, LDL-C, HDL-C, TG, total/HDL-C ratio, Lp(a), Apo B, Apo A-I; proportion of patients attaining HDL-C ≥40 mg/dl, TG <150 mg/dl, or NCEP ATP III CHD risk=adjusted goals for non-HDL-C and LDL-C	Primary: Flushing was the most common treatment-related adverse event. 71% of patients experienced flushing and 92% of flushing episodes were mild or moderate in intensity. Other adverse events that were considered related to treatment that occurred in ≥3% of patients included pruritus, nausea, elevated A1C, elevated CPK, and elevated blood glucose. Twenty-three percent of patients discontinued treatment because of a treatment-related adverse event. Flushing contributed to 7% of patients discontinuing treatment. Median changes in lipid parameters from baseline to 24 weeks were: non-HDL-C -27.3%, LDL-C -25%, HDL-C +23.9%, and TG -35.9% (P<0.0001 vs baseline). For patients who failed to achieve target lipid levels following simvastatin monotherapy, 82% of patients achieved their CHD risk-adjusted NCEP ATP III non-HDL-C goal, 85% reached their CHD risk-adjusted NCEP ATP III LDL-C goal, 67% reached their CHD risk-adjusted NCEP ATP III HDL-C goal, 64% reached their CHD risk-adjusted NCEP ATP III TG goal.
Stein et al.[40] (2007) Rosuvastatin 40 mg	MC, OL Adult patients ≥18 years of age with	N=1,380 ≤96 weeks	Primary: Percentage of patients who achieved NCEP	Primary: At 12 weeks, 83% of patients achieved the NCEP ATP III LDL-C goal (95% CI, 81% to 85%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for ≤96 weeks, after a 6-week dietary lead-in period	LDL-C ≥190 and ≤260 mg/dL and TG <400 mg/dL; patients were excluded if they had homozygous familial hypercholesterolemia, significant liver enzyme elevations, active arterial disease within the previous 3 months, uncontrolled hyper-tension, serum CK >3 times ULN, serum creatinine >2.5 mg/dL, uncontrolled diabetes or hypothyroidism		ATP III LDL-C goals (<160, <130, or <100 mg/dL) at 12 weeks Secondary: Reduction in LDL-C, HDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B	Secondary: At 48 weeks, rosuvastatin therapy was associated with a significant reduction from baseline in LDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B (P<0.0001). At 48 weeks, rosuvastatin therapy was associated with a significant increase from baseline in HDL-C (11%; P<0.0001). During the 96-week study period, 13% of patients experienced a serious adverse event, 0.4% of these patients died, and 2% of the patients experienced myalgia.
Wolffenbuttel et al.[42] (2005) CORALL Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 20 mg daily for 6 weeks, titrated to 40 mg daily for 6 weeks vs atorvastatin 20 mg	MC, OL, PG, R Adult patients ≥18 years of age with type 2 diabetes for ≥3 month, LDL ≥3.36 mmol/L in statin naïve patients or LDL between 2.99 mmol/L and 5.0 mmol/L in patients exposed to statin therapy within the previous 4 weeks, TG <4.52 mmol/L, and A1C<10%	N=265 24 weeks	Primary: Reduction in LDL-C, HDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B, percentage of patients who achieved LDL-C goals (<2.6 mmol/L or <2.5 mmol/L) at 18 weeks	Primary: Both rosuvastatin and atorvastatin were associated with a significant reduction from baseline in LDL-C, apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, TG, and apo B (P<0.001). Rosuvastatin therapy was associated with significant reduction in LDL-C (P<0.01), apolipoprotein ratio (P<0.05), LDL:HDL ratio (P<0.01), TC (P<0.05), TC:HDL ratio (P<0.05), non–HDL-C(P<0.05), and apo B (P<0.05), compared to atorvastatin therapy. Significantly greater percentage of patients randomized to rosuvastatin therapy achieved LDL-C goals at 18 weeks of therapy compared with the control (P<0.05). The incidence of treatment-related adverse events was similar in the rosuvastatin and atorvastatin groups (47% vs 50%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 40 mg daily for 6 weeks, titrated to 80 mg daily for 6 weeks				
Deedwania et al.[43] (2007) IRIS Rosuvastatin 10 mg daily for 6 weeks, after a 6-week dietary lead-in period vs rosuvastatin 20 mg daily for 6 weeks, after a 6-week dietary lead-in period vs atorvastatin 10 mg daily for 6 weeks, after a 6-week dietary lead-in period vs atorvastatin 20 mg	MC, OL, R South-Asian patients ≥18 years of age with CHD or CHD risk equivalent and LDL-C ≥100 mg/dL or ≥2 risk factors, 10-year CHD risk 10%-20%, and LDL-C ≥130 mg/dL or 0-1 risk factor and LDL-C ≥160 mg/dL, LDL-C had to be within 15% of each other and ≤300 mg/dL on 2 consecutive measurements, with TG <500 mg/dL	N=740 12 weeks	Primary: Percentage change in LDL-C from baseline at 6 weeks Secondary: Achievement of NCEP ATP III LDL-C goals, percentage change from baseline in non–HDL-C, HDL-C, TC, TG, and safety	Primary: At 6 weeks, patients randomized to the rosuvastatin 10 mg group experienced a significant reduction in LDL-C from baseline compared with atorvastatin 10 mg therapy (P=0.0023). The difference in LDL-C reduction from baseline at 6 weeks between the rosuvastatin 20 mg and atorvastatin 20 mg groups was not statistically significant. Secondary: The proportion of patients achieving NCEP ATP III LDL-C goals was similar in the rosuvastatin 10 mg and 20 mg and atorvastatin 10 mg and 20 mg groups (79%, 89%, 76%, and 85%, respectively). At 6 weeks, patients randomized to the rosuvastatin 10 mg group experienced a significant reduction in LDL-C:HDL-C ratio from baseline compared with atorvastatin 10 mg therapy (P<0.017). There were no clinically relevant differences between statins in adverse events or incidence of creatine kinase >10 times the ULN, ALT>3 times the ULN, proteinuria, or hematuria over a 6-week study period.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 6 weeks, after a 6-week dietary lead-in period				
Betteridge et al.[44] (2007) ANDROMEDA Rosuvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks vs atorvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks	DB, MC, PG, RCT Adult patients ≥18 years of age, with type 2 diabetes, with ≥2 FBG levels of ≥7.0 mmol/L, and a triglyceride level of ≤6.0 mmol/L	N=509 16 weeks	Primary: Percentage changes from baseline in LDL-C levels at 16 weeks Secondary: Percentage changes from baseline in: LDL-C, TC, HDL-C, TG, non–HDL-C, cholesterol ratios, apo B, apolipoprotein ratio, A1C, the proportion of patients achieving 2003 Joint European Societies LDL-C (<2.5 mmol/L) and TC (<4.5 mmol/L) goals	Primary: Rosuvastatin therapy was associated with a statistically significant reduction in LDL-C from baseline compared with atorvastatin therapy (57.4% vs 46%; P=0.001). Secondary: Rosuvastatin therapy was associated with a statistically significant reduction in apolipoprotein ratio, LDL:HDL ratio, TC, TC:HDL ratio, non–HDL-C, and apo B from baseline compared with atorvastatin therapy (P<0.001). Rosuvastatin therapy was associated with a statistically significant reduction in A1C from baseline compared with atorvastatin therapy (P=0.049). A higher percentage of patients randomized to rosuvastatin therapy were able to reach the 2003 Joint European Societies LDL-C goal compared to the atorvastatin group at 16 weeks of therapy (95.6% vs 87.3%; P=0.002). A higher percentage of patients randomized to rosuvastatin therapy were able to reach the 2003 Joint European Societies TC goal compared to the atorvastatin group at 16 weeks of therapy (93.4% vs 86%; P=0.01).
Betteridge et al.[45] (2007) ANDROMEDA Rosuvastatin 10 mg daily for 8 weeks, after a 4-week	DB, DD, MC, PG, RCT Subanalysis of ANDROMEDA study. Adult patients ≥18 years of age, with type 2 diabetes, with	N=509 16 weeks	Primary: A composite end point of CRP <2mg/L and LDL-C <70 mg/dL	Primary: Rosuvastatin therapy was associated with a statistically significant reduction in the primary end point from baseline compared with atorvastatin therapy (58% vs 37%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
washout period, titrated up to 20 mg daily for another 8 weeks vs atorvastatin 10 mg daily for 8 weeks, after a 4-week washout period, titrated up to 20 mg daily for another 8 weeks	≥2 FBG levels of ≥7.0 mmol/L, and a triglyceride level of ≤6.0 mmol/L (see above for exclusion criteria)			
Ferdinand et al.[46] (2006) ARIES Rosuvastatin 10 mg one daily for 6 weeks, after a 6-week lead-in period vs rosuvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period	OL, R African-American adult patients ≥18 years of age with LDL ≥160 mg/dL but ≤300 mg/dL, TG <400. Patients were excluded if they had a history of homozygous familial hypercholesterolemia, type I, III, or V hypercholesterolemia, active arterial disease, uncontrolled hypertension, poorly controlled diabetes, active liver disease, transaminase elevation, bilirubin levels ≥2 times the ULN, unexplained	N=774 6 weeks	Primary: The change from baseline in LDL-C at 6 weeks Secondary: Changes from baseline in other lipids, apolipoproteins	Primary: Patients in the rosuvastatin group experienced a statistically significant reduction in LDL-C levels compared to the atorvastatin groups (P<0.017). Secondary: Patients in the rosuvastatin group experienced a statistically significant reduction in TC, non–HDL-C levels, apo B concentrations, lipoprotein, and apolipoprotein ratios compared to the atorvastatin groups (P<0.017). Patients in the rosuvastatin group experienced a statistically significant increase in HDL-C levels compared to the atorvastatin groups (P<0.017). Side effects were similar in the rosuvastatin and atorvastatin treatment groups (34.4% and 33.6%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period	serum creatine kinase levels >3 times the ULN, or serum creatinine 2.0 mg/dL.			
Lloret et al.[47] (2006) STARSHIP Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs rosuvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 10 mg once daily for 6 weeks, after a 6-week lead-in period vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week lead-in period	MC, OL, RCT Hispanic-American adult patients ≥18 years of age with a 10-year risk >10% for CHD, current CHD or its equivalent, LDL ≥130 mg/dL but ≤300 mg/dL on two measurements within 15% of each other, TG <400	N=696 6 weeks	Primary: Percent change from baseline in LDL-C at 6 weeks Secondary: Proportion of patients reaching NCEP ATP III lipid goals, percent change from baseline in TC, apo B, non–HDL-C, TG, HDL, apo AI, LDL:HDL-C ratio, TC:HDL ratio, apo B:apo AI ratio, side effects at 6 weeks	Primary: Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in LDL-C from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (45%, 50%, 36%, and 42%, respectively; P<0.0001). Secondary: More patients randomized to the rosuvastatin 10 mg and 20 mg groups achieved NCEP ATP III LDL-C goals compared to the atorvastatin 10 mg and 20 mg groups at 6 month (78%, 88%, 60%, 73%, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in TC from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (P<0.0001, P<0.01, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in apo B from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (P<0.0001, P<0.017, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in LDL:HDL cholesterol ratio from baseline compared to the atorvastatin 10 mg and 20 mg groups, respectively, at 6 month (P<0.0001). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in TC:HDL cholesterol from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (P<0.0001, P<0.01, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in non-HDL:HDL cholesterol from baseline compared to the atorvastatin 10 mg and 20 mg groups at 6 month (P<0.0001, P<0.01, respectively). Patients randomized to the rosuvastatin 10 mg and 20 mg groups experienced a statistically significant reduction in apo B:apo AI from baseline compared to the atorvastatin 10 mg and 20 mg groups, respectively, at 6 month (P<0.01). Side effects were similar across treatment groups. There were no cases of myopathy, rhabdomyolysis, or clinically significant increases in serum creatine kinase.
Faergeman et al.[175] (2008) ECLIPSE Rosuvastatin 10 mg for 6 weeks; dose was force-titrated every 6 weeks to maximal dose (40 mg) vs atorvastatin 10 mg for 6 weeks; dose was force-titrated every 6 weeks to maximal dose (80 mg) Doses could be decreased for safety reasons.	RCT, OL, MC, PG Patients ≥18 years of age with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis or a 10-year CHD risk score >20% (CHD risk equivalent)	N=1,036 24 weeks	Primary: Percentage of patients achieving NCEP ATP III LDL-C goal <100 mg/dl after 24 weeks Secondary: Percentage of patients achieving NCEP ATP III LDL-C goal <100 mg/dl at weeks 6, 12 and 18; achievement of the following NCEP ATP III goals at all time points: non-HDL-C <130 mg/dl, 2003 European LDL-C goals (100-115 mg/dl and	Primary: A greater percentage of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin than with atorvastatin at week 24 (83.6% vs 74.6%; P<0.001). Secondary: A greater percentage of patients achieved the NCEP ATP III non-HDL-C goal with rosuvastatin than with atorvastatin (week 6, 41.9% vs 19.6%; week 12, 64.5% vs 32.0%; week 18, 76.0% vs 55.0%; week 24, 79.6% vs 68.0%; P<0.02 at each time point). A greater percentage of patients achieved the 2003 European LDL-C goals and the combined LDL-C and TC goals with rosuvastatin than with atorvastatin at all time points (P<0.001). Significantly greater reductions in LDL-C, TC and non-HDL-C levels, and increases in HDL-C were achieved with rosuvastatin than with atorvastatin at all time points. The reductions in TG levels were similar in both treatment groups at all time points except at week 24, when a significantly greater decrease was observed in patients receiving atorvastatin compared with those receiving rosuvastatin (P<0.05). Significantly greater mean reductions in LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I ratios were achieved with rosuvastatin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			combined LDL-C and TC goals (LDL-C 100-115 mg/dl and TC 175 or 190 mg/dl), percentage changes from baseline in LDL-C, HDL-C, TC, TG, non-HDL-C, and lipid ratios	than with atorvastatin at all time points (P<0.001). Adverse events (AE) were experienced by 53.7% and 52.5% of patients receiving rosuvastatin and atorvastatin, respectively. Myalgia was the most frequently reported AE.
Insull et al.[48] (2007) SOLAR Rosuvastatin 10 mg daily for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs atorvastatin 10 mg for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not	MC, RCT Patients were 18 years or older, enrolled in a managed care health plan, and classified as high risk by NCEP ATP III risk assessment	N=1,632 12 weeks	Primary: Achievement of the NCEP ATP III high-risk LDL-C goal (<100 mg/dL) at week 6 Secondary: Proportions of patients who reached the high-risk LDL-C goal at 12 weeks, proportions of hypertriglyceridemic patients who achieved both the LDL-C goal (<100 mg/dL) and the non–HDL-C goal (<130 mg/dL) for high-risk patients, and changes in LDL-C and other lipid parameters at 6 and 12 weeks	Primary: Significantly greater proportion of patients randomized to rosuvastatin achieved their LDL-C target compared with the atorvastatin and simvastatin arms at 6 weeks of therapy (65%, 41%, and 39%, respectively; P<0.001). Secondary: After 12 weeks, 76% of patients taking rosuvastatin reached the LDL-C goal compared with 58% and 53% of patients on atorvastatin and simvastatin, respectively (P<0.001). After 6 weeks, 44% of hypertriglyceridemic patients taking rosuvastatin reached the combined LDL-C/non–HDL-C goals compared with 19% of patients on simvastatin, respectively (P<0.001). After 12 weeks, 57% of hypertriglyceridemic patients taking rosuvastatin reached the combined LDL-C/non–HDL-C goals compared with 31% of patients on simvastatin, respectively (P<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in LDL-C from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (P<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TC level from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
achieved vs simvastatin 20 mg for 6 weeks, after a 6-week lead-in period, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved				Patients randomized to rosuvastatin experienced a statistically significant reduction in non–HDL-C level from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (P<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in non–HDL-C:HDL-C ratio from baseline compared to the atorvastatin and simvastatin groups at 6 and 12 months (P<0.001). Patients randomized to rosuvastatin experienced a statistically significant increase in HDL-C from baseline compared to the atorvastatin and simvastatin groups at 12 months (P<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TG from baseline compared to the simvastatin group at 6 and 12 months (P<0.001). The frequency and types of adverse events were similar in all treatment groups.
Leiter et al.[49] (2007) POLARIS Rosuvastatin 40 mg once daily vs atorvastatin 80 mg once daily	DB, PG, R Patients between 45-80 years of age, with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis, or a 10-year Framingham CHD-risk score >20%, with LDL-C ≥160 but <250 mg/dL, and TG <400 mg/dL	N=871 26 weeks	Primary: The percentage change from baseline in LDL-C levels at week 8 Secondary: Safety, the percentage change from baseline in LDL-C levels at week 26, the percentage change from baseline in other lipids and lipoproteins at weeks 8 and 26, and the proportion	Primary: Rosuvastatin 40 mg was associated with a significantly greater reduction in LDL-C from baseline at 8 weeks compared to atorvastatin 80 mg therapy (56% vs 52%; P<0.001). Secondary: Rosuvastatin 40 mg was associated with a significantly greater reduction in LDL-C from baseline at 26 weeks compared to atorvastatin 80 mg therapy (57% vs 53%). Rosuvastatin 40 mg was associated with a significantly greater reduction in TG (27% vs 22.2%; P<0.05), non–HDL-C (50.8% vs 48.3%; P<0.01), LDL-C:HDL-C ratio (58.5% vs 53.6%; P<0.001), TC:HDL-C (44.4% vs 41.1%; P<0.001), non–HDL-C:HDL-C (53.6% vs 49.6%; P<0.001), apo B (44.6% vs 42.3%; P<0.05), and apo AI (4.2% vs –0.5%; P<0.001) from baseline at 8 weeks compared to atorvastatin 80 mg therapy. Rosuvastatin 40 mg was associated with a significantly greater increase in HDL-C from baseline at 8 weeks compared to atorvastatin 80 mg therapy

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			of patients reaching NCEP ATP III and 2003 European lipid goals at 8 and 26 weeks	(9.6% vs 4.4%; P<0.001). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved the NCEP ATP III LDL-C goal of <100 mg/dL compared with patients in the atorvastatin group (80% vs 72%; P<0.01). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved NCEP ATP III LDL-C goal of <70 mg/dL compared with patients in the atorvastatin group (36 vs 18%; P<0.001). At 6 weeks of therapy, more patients in the rosuvastatin 40 mg group achieved the 2003 European lipid goals compared with patients in the atorvastatin group (79% vs 69%; P<0.001). The incidence of drug-related adverse effects was low in both rosuvastatin and atorvastatin treatment groups (0.5% vs 0.2%).
Jones et al.[50] (2003) STELLAR Rosuvastatin once daily vs pravastatin once daily vs atorvastatin once daily vs simvastatin once daily	OL, PG Men and nonpregnant women ≥18 years of age with hypercholesterolemia, with LDL-C level ≥160 and <250 mg/dL at the 2 most recent consecutive visits	N=2,431 6 weeks	Primary: Percent change in LDL-C from baseline to 6 weeks Secondary: Percent change in HDL-C, triglyceride, and TC levels	Primary: Compared to all doses of atorvastatin and pravastatin, rosuvastatin was associated with a greater reduction in LDL-C from baseline (P<0.001 for both). When compared to baseline, the following changes in LDL-C were observed: a 45.8% to 55.0% reduction with rosuvastatin, a 36.8% to 51.1% reduction with atorvastatin, a 28.3% to 45.8% reduction with simvastatin, and a 20.1% to 29.7% reduction with pravastatin. The highest LDL reductions observed were a 55% reduction achieved in the rosuvastatin 40 mg group and a 51% reduction achieved in the atorvastatin 80 mg group (P=0.006). Secondary: A 7.7% to 9.6% increase in HDL, a 19.8% to 26.1% reduction in TG, and a 32.9% to 40.2% reduction in TC was observed with rosuvastatin 10 mg to 40 mg group. A 2.1% to 5.7% increase in HDL, 20.0% to 28.2% reduction in TG, and a 27.1% to 38.9% reduction in TC was observed with the atorvastatin 10 mg to 80 mg group.

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(treatments ranged from 10 mg to 80 mg)				A 5.2% to 6.8% increase in HDL, 11.9% to 18.2% reduction in TG, and a 20.3% to 32.9% reduction in TC was observed with the simvastatin 10 mg to 80 mg group. A 3.2% to 5.6% increase in HDL, 7.7% to 13.2% reduction in TG, and a 14.7% to 21.5% reduction in TC was observed with the pravastatin 10 mg to 40 mg group.
Stalenhoef et al.[51] (2005) Rosuvastatin 10 mg daily for 6 weeks, titrated up to rosuvastatin 20 mg daily for another 6 weeks vs atorvastatin 10 mg daily for 6 weeks, titrated up to atorvastatin 20 mg daily for another 6 weeks vs placebo daily for 6 weeks, followed with rosuvastatin 20 mg daily for another 6 weeks	DB, DD, MN, PG, RCT Men and women aged ≥18 years with metabolic syndrome (defined as at least 3 of the following: waist circumference >102 cm for men and >88 cm for women, TG ≥1.70 mmol/L, HDL-C <1.04 mmol/L for men and <1.30 mmol/L for women, BP ≥130/85 mm Hg or receiving antihypertensive therapy, FBG ≥6.11 mmol/L), LDL-C ≥3.36 mmol/L, and 10-year CHD risk score of >10%	N=401 12 weeks	Primary: Percentage change from baseline in LDL-C at 6 weeks Secondary: Percentage change from baseline in TC, LDL-C, HDL-C, non–HDL-C at 12 weeks	Primary: Rosuvastatin 10 mg reduced LDL-C significantly more than placebo (42.7% vs 0.3%, respectively; P<0.001) after 6 weeks of therapy. At 6 weeks, rosuvastatin had a significantly greater percentage change in LDL-C levels from baseline compared to atorvastatin (41.7% vs 35.7%, respectively; P<0.001). Secondary: At 12 weeks, significant reductions in LDL-C were observed in the rosuvastatin combined group in comparison to the atorvastatin group (48.9% vs 42.5%, respectively; P<0.001). Significantly more patients taking rosuvastatin achieved LDL-C goal (3.0 mmol/L) than patients taking atorvastatin at both 6 weeks (P<0.05) and 12 weeks (P<0.05). Percentage improvements in TC (P<0.001), HDL-C (P<0.01), and non–HDL-C(P<0.001) from baseline were significantly greater in patients taking rosuvastatin compared to patients taking atorvastatin at both 6 and 12 weeks.
Ballantyne et al.[52] (2006)	MC, OL, R Patients ≥18 years of	N=1,993 16 weeks	Primary: The proportion of patients achieving	Primary: At 16 weeks, more patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL compared to patients who

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MERCURY II Rosuvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs atorvastatin 10 mg daily for 8 weeks after a 6-week dietary lead-in period vs atorvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs simvastatin 20 mg daily for 8 weeks after a 6-week dietary lead-in period vs simvastatin 40 mg daily for 8 weeks after a 6-week	age, at high risk for CHD events, fasting LDL-C level ≥130 to <250 mg/dL on two separate measurements within 15% of each other, and a fasting TG <400 mg/dL		LDL-C<100 mg/dL at week 16 Secondary: The proportion of patients meeting the LDL-C target at week 8, change in lipid and lipoprotein measures at weeks 8 and 16, adverse events	received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg for the duration of the study (83%, 42%, 64%, 32%, and 56%, respectively). At 16 weeks, significantly more patients who switched to rosuvastatin therapy achieved LDL-C target level <100 mg/dL compared to patients who remained on their initial medication regimen (P<0.001). Secondary: At 16 weeks, patients who switched to rosuvastatin therapy experienced a significant LDL-C reduction from baseline compared to patients remaining on their initial medication regimen (P<0.001). At 8 weeks, significantly more patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (82%, 43%, 62%, 33%, and 55%, respectively; P<0.0001). At 16 weeks, significantly more patients randomized to rosuvastatin therapy were able to achieve LDL-C level <70 mg/dL compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (37%, 7%, 13%, 1%, and 10%, respectively). At 16 weeks, patients who switched to rosuvastatin therapy experienced a significant atherogenic lipid measure and ratio reduction from baseline compared to patients remaining on their initial medication regimen (P<0.001). At 16 weeks, significantly more hypertriglyceridemic patients randomized to rosuvastatin therapy were able to achieve LDL-C target level <100 mg/dL and non–HDL-C targets compared to patients who received atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (80%, 20%, 42%, 19%, and 29%, respectively). The frequency and type of adverse events were similar in all treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dietary lead-in period After 8 weeks of treatment, patients received an additional 8 weeks of either initial or rosuvastatin therapy.				groups. In addition, there were no symptomatic adverse events associated with hepatic dysfunction.
Milionis et al.[54] (2006) ATOROS Rosuvastatin 10 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 20 mg daily for 18 weeks vs atorvastatin 20 mg once daily for 6 weeks, after a 6-week dietary lead-in period, titrated to 40 mg daily for 18 weeks	OL, PG, R Patients, average age of 53.6 years, free of symptomatic ischemic heart disease or any other clinically evident heart disease, at moderate risk for CHD according to NCEP ATP classification, with baseline TC >240 mg/dL, and TG <350 mg/dL	N=180 24 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<130 mg/dL) Secondary: Change from baseline in LDL-C, HDL-C, TC, TG, non-HDL, and apo B at 24 weeks	Primary: At 6 weeks, 75% and 71.7% of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin and atorvastatin therapies, respectively. Secondary: Both rosuvastatin and atorvastatin were associated with statistically significant reductions in LDL from baseline (48.7% vs 44.6%; P<0.001). Rosuvastatin therapy was associated with a significant 5% increase from baseline in HDL-C (P<0.001). Atorvastatin therapy was associated with a significant 2.1% reduction from baseline in HDL-C (P<0.001). Compared to atorvastatin, rosuvastatin was associated with a significantly greater increase in HDL-C (P=0.002). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in TC from baseline (36.1% vs 36.9%; P<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in TG from baseline (29% vs 27.8%; P<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in non-HDL from baseline (45% vs 46%; P<0.001). Both rosuvastatin and atorvastatin were associated with statistically significant reductions in apo B from baseline (29% vs 26%; P<0.001). The incidence of myalgia was similar in both treatment groups (3 %). There were no reports of significant ALT or CK elevations.
Clearfield et al.[55]	OL, PG, R, MC	N=996	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) PULSAR Rosuvastatin 10 mg once daily for 6 weeks vs atorvastatin 20 mg once daily for 6 weeks	Patients ≥18 years of age with hypercholesterolemia and either a history of CHD or a CHD-risk equivalent, with the mean of the two most recent LDL levels (within 15% of each other) ≥130 mg/dL and <220 mg/dL, as well as TG <400 mg/dL	6 weeks	Percentage change from baseline in LDL-C at 6 weeks Secondary: Percentage of patients achieving the NCEP ATP III and the 2003 European LDL-C goals (<100 mg/dL), the 2003 European LDL-C goal for patients at greatest risk (CVD, diabetes, LDL-C ≥6mmol/L, TC ≥8 mmol/L, or blood pressure ≥180/110 mm Hg), the NCEP ATP III non-HDL-C goal (<130 mg/dL, combined LDL-C:TC goal <175-190 mg/dL, the percentage change from baseline in HDL-C, TC, TG, non-HDL-C, apo B, LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C, lipoprotein(a) frequency and severity of adverse events	Compared to atorvastatin, rosuvastatin was associated with a statistically greater reduction from baseline in LDL-C at 6 weeks (42.7% vs 44.6%; P<0.05). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP ATP III and the 2003 European LDL-C goals, compared with the atorvastatin-treated group (68% vs 63%; P<0.05). In addition, more rosuvastatin-treated patients at greatest risk for CHD reached the 2003 European LDL-C goals, compared to patients treated with atorvastatin (65.6% vs 60.3%; P>0.05). While more patients reached the NCEP ATP III non–HDL-C goal with rosuvastatin compared with atorvastatin, the difference was not statistically significant (69.7% vs 65%; P>0.05). While more patients reached the NCEP ATP III combined LDL-C:TC goal with rosuvastatin compared with atorvastatin, the difference was not statistically significant (55.2% vs 53.3%; P>0.05). Rosuvastatin was associated with a statistically significant increase in HDL-C from baseline compared to atorvastatin (6.4% vs 3.1%; P<0.001). There was no statistically significant difference in the change from baseline in TC, TG, non–HDL-C, and apo B observed with rosuvastatin and atorvastatin (P>0.05). Rosuvastatin was associated with a statistically significant reduction in LDL-C:HDL-C from baseline compared to atorvastatin (47.6% vs 44%; P<0.001). Rosuvastatin was associated with a statistically significant reduction in TC:HDL-C from baseline compared to atorvastatin (34.6% vs 32.3%; P<0.01). Rosuvastatin was associated with a statistically significant reduction in non-HDL-C:HDL-C from baseline compared to atorvastatin (43.3% vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				40.2%; P<0.001). Atorvastatin was associated with a statistically significant increase in lipoprotein(a) from baseline compared to rosuvastatin (13.3% vs 2.1%; P<0.001). The frequency and type of adverse events were similar with the rosuvastatin and atorvastatin groups (27.5% vs 26.1%). The most commonly reported adverse effects were myalgia and urinary tract infections.
Rosenson et al.[174] (2009) Rosuvastatin 10 mg once daily for 6 weeks, followed by 20 mg thereafter vs atorvastatin 10 mg once daily for 6 weeks, followed by 20 mg thereafter vs placebo	RCT, DB, MC, PC Patients ≥18 years of age with the metabolic syndrome, LDL-C 130–250 mg/dl and a 10-year CHD risk score >10%	N=318 12 weeks	Primary: Lipoprotein particle concentrations	Primary: After 6 weeks of therapy, rosuvastatin 10 mg and atorvastatin 10 mg significantly reduced LDL-C, LDL particle concentration, apo B, and non-HDL-C compared with placebo (P<0.001). Rosuvastatin significantly reduced LDL-C (P<0.001), LDL particle concentration (P<0.05), and non-HDL-C (P<0.01) compared to atorvastatin after 6 and 12 weeks. After 6 weeks of therapy, rosuvastatin 10 mg and atorvastatin 10 mg significantly reduced VLDL particle concentration and serum triglycerides compared with placebo (P<0.001). There was no difference between the two statins on either end point at week 6 or 12. After 6 weeks of therapy, rosuvastatin 10 mg increased HDL particle concentration (15%) and HDL-C (10%) compared to placebo (P<0.001). Atorvastatin significantly increased HDL particle concentration compared to placebo (6%, P=0.013); however, there was no difference in HDL-C (4%, P=0.45). Rosuvastatin significantly increased HDL particle concentration and HDL-C compared to atorvastatin after 6 and 12 weeks (P≤0.002). Neither statin showed a significant effect on apo A-I compared with placebo; however, increases in apo A-I were significantly greater with rosuvastatin than atorvastatin at 6 and 12 weeks (P=0.001 and P=0.02, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				A higher proportion of patients receiving rosuvastatin achieved LDL-C <100 mg/dl compared to atorvastatin at 6 and 12 weeks (P<0.01 and P<0.0001, respectively). Patients receiving rosuvastatin achieved LDL particle concentration <1,300 nmol/l at 12 weeks (P=0.02) and <1,000 nmol/l at 6 weeks (P=0.02) compared to atorvastatin. The percentage of patients who attained LDL particle concentration <1,300 nmol/l was similar to that achieving LDL cholesterol <100 mg/dl.
Bullano et al.[56] (2007) Rosuvastatin (11 mg mean daily dose) vs atorvastatin (15 mg mean daily dose)	RETRO Patients ≥18 years of age, initiated on rosuvastatin or atorvastatin between August 1, 2003 and September 30, 2004 with at least one lipid level (LDL-C, TG, HDL-C, TC) obtained prior to and posttherapy initiation	N=453 Up to 79 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Percentage of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), the percentage change from baseline in HDL-C, TC, TG, non-HD-CL	Primary: Patients treated with rosuvastatin experienced a statistically greater percent reduction in LDL-C from baseline compared with the atorvastatin-treated group (35% vs 26%; P<0.001). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP ATP III LDL-C goals, compared with the atorvastatin-treated group, when adjusted for age, sex, LDL-lowering required to reach goal, risk category, and duration of therapy (74% vs 65%; P<0.05). Unadjusted attainment rates were similar in both treatment groups (P=0.088). Moreover, patients in the rosuvastatin group required greater LDL-C reduction to reach their LDL goal compared to patients treated with atorvastatin (26.3% vs 23.5%; P<0.05). In addition, significantly more patients in the rosuvastatin groups reached the updated, optional NCEP ATP III LDL-C goals, compared to atorvastatin group (61% vs 48%; P<0.05). There was no statistically significant difference between the change in HDL-C obtained with rosuvastatin and atorvastatin (P=0.234). Patients treated with rosuvastatin experienced a statistically greater percent reduction in TC from baseline compared with the atorvastatin-treated group (26% vs 20%; P<0.001). There was no statistically significant difference between the TG reduction obtained with rosuvastatin and atorvastatin (P=0.192). Patients treated with rosuvastatin experienced a statistically greater

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				percent reduction in non–HDL-C from baseline compared with the atorvastatin-treated group (33% vs 25%; P<0.001).
Ai et al.[58] (2008) STELLAR Rosuvastatin 40 mg daily for 6 weeks vs atorvastatin 80 mg daily for 6 weeks	OL Patients ≥18 years of age, with hypercholesterolemia, with LDL-C levels ≥160 mg/dL and <250 mg/dL, as well as TG <400 mg/dL	N=271 6 weeks	Primary: Change in direct LDL-C and small dense LDL-C Secondary: Percentage change from baseline in HDL-C, TC, TG, non-HDL-C, TC:HDL-C ratio	Primary: Rosuvastatin was associated with a significant reduction from baseline in direct LDL-C compared with atorvastatin (52% vs 50%; P=0.01). Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared with atorvastatin (53% vs 46%; P<0.001). Secondary: Rosuvastatin was associated with a significant increase from baseline in HDL-C compared with atorvastatin (10% vs 2%; P<0.001). There was no statistically significant difference between the TC reduction obtained with rosuvastatin and atorvastatin (P=0.10). There was no statistically significant difference between the TG reduction obtained with rosuvastatin and atorvastatin (P=0.50). Rosuvastatin was associated with a significant reduction from baseline in non–HDL-C compared with atorvastatin (51% vs 48%; P<0.0078). Rosuvastatin was associated with a significant reduction from baseline in TC:HDL-C compared with atorvastatin (46% vs 39%; P<0.001).
Mazza et al.[173] (2008) Rosuvastatin 10 mg once daily vs atorvastatin 20 mg once daily	RCT, OL Patients 18 to 65 years of age with primary hypercholesterolemia (LDL-C >200 mg/dL) and at high risk for coronary heart disease	N=106 48 weeks	Primary: Plasma levels of TC, TG, LDL-C HDL-C, non-HDL-C	Primary: After 48 weeks of treatment, atorvastatin significantly lowered TC, LDL-C, and non HDL-C levels (-21.6%; -30%; -26.98%, respectively; P<0.001 combined). HDL-C levels increased +4.52% (P=NS) TG levels decreased -4.62% (P=NS). After 48 weeks of treatment, rosuvastatin significantly lowered TC, LDL-C, non HDL-C, and TG levels (-35.77%, -44.32%, -43.12%, -36.41%, respectively; P<0.001 combined). HDL-C level also decreased -2.04% (P=NS). Rosuvastatin was more effective than atorvastatin in reducing plasma levels of TC, LDL-C, non-HDL-C and TG (-35.77%, -44.32%, -43.12%,

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				-36.41%, respectively, with rosuvastatin vs -21.62%, -30%, -26.98%, -4.62%, respectively, with atorvastatin; P<0.005). Both drugs had no significant effect on plasma HDL-C levels relative to baseline. There were no significant differences in either treatment group in parameters related to safety.
Bullano et al.[57] (2006) Rosuvastatin 5-40 mg daily vs other statins (atorvastatin 10-80 mg/day, simvastatin 5-80 mg/day, pravastatin 10-80 mg/day, lovastatin 10-80 mg/day, fluvastatin 20-160 mg/day)	RETRO Patients ≥18 years of age, initiated on a statin between August 1, 2003 and September 30, 2004 with at least one LDL-C level obtained prior to and after therapy initiation	N=8,251 Up to 122 days of therapy	Primary: Percentage change from baseline in LDL-C Secondary: Percentage of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), the percentage change from baseline in HDL-C, TC, and TG	Primary: Patients treated with rosuvastatin experienced a statistically greater percent reduction in LDL-C from baseline compared with other statin groups (33% vs atorvastatin 24%, simvastatin 20%, pravastatin 18%, fluvastatin 13% and lovastatin 16%; P<0.05). Moreover, rosuvastatin 10 mg was associated with a greater percentage of LDL-C reduction from baseline compared to either atorvastatin 10-20 mg (P<0.05) or simvastatin 10-20 mg (P<0.05). Secondary: Significantly more patients in the rosuvastatin group achieved NCEP ATP III LDL-C goals, compared with the other statin treatment groups (P<0.05). Moreover, patients in the rosuvastatin group required greater LDL-C reduction to reach their LDL goal compared to patients treated with other statins (29% vs 23-27%; P<0.05). In addition, significantly more patients in the rosuvastatin groups reached the updated, optional NCEP ATP III LDL-C goals, compared to other statins (58% vs 29-48%; P<0.05). There was no statistically significant difference between the HDL-C reduction obtained with rosuvastatin and other statins (P>0.05). Patients treated with rosuvastatin experienced a statistically greater percent reduction in total cholesterol from baseline compared with other statin groups (24% vs atorvastatin 18%, simvastatin 14%, pravastatin 13%, fluvastatin 10%, and lovastatin 12%; P<0.05). Patients treated with rosuvastatin experienced a statistically greater percent reduction in TG from baseline compared with other statin groups (11% vs simvastatin 6%, pravastatin 4%, fluvastatin 4%, and lovastatin 5%; P<0.05). However there was no statistically significant difference in

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				TG reduction from baseline between rosuvastatin and atorvastatin-treated groups (11% vs 10%; P>0.05).
Fox et al.[59] (2007) Rosuvastatin vs other statins (atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin)	RETRO Adult patients with diabetes (ICD 9 code 250, on antidiabetic medication, or FBG >126 mg/dL), newly prescribed a statin between August 2003 and March 2006	N=4,754 Variable duration	Primary: Percent reduction in LDL-C from baseline, percentage of patients achieving LDL-C goal <100 mg/dL	Primary: Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared with atorvastatin (22.5%), simvastatin (20.1%), pravastatin (13.7%), lovastatin (17.3%), and fluvastatin (15.8%) (P<0.0001). Compared to other statins, a greater percentage of patients receiving rosuvastatin were able to reach their LDL-C goal <100 mg/dL (P<0.05).
Harley et al.[60] (2007) Rosuvastatin after simvastatin therapy (5-80 mg) vs atorvastatin after simvastatin therapy (5-80 mg) vs lovastatin after simvastatin monotherapy (5-80 mg) vs	RETRO Adult patients ≥18 years of age, receiving simvastatin monotherapy between July 2005 and June 2006, switched to other statin therapy	N=134,160 1 year	Primary: Percentage of patients achieving NCEP ATP III LDL goal after switching from simvastatin to another statin	Primary: Of those patients not at NCEP ATP III LDL goal with simvastatin monotherapy, 73% reached their LDL goal following the switch to another statin.

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pravastatin after simvastatin monotherapy (5-80 mg) vs fluvastatin after simvastatin monotherapy (5-80 mg) vs simvastatin in combination with ezetimibe after simvastatin monotherapy (5-80 mg)				
Fox et al.[61] (2007) Rosuvastatin switch vs simvastatin switch	RETRO Adult patients ≥18 years of age switching to either rosuvastatin or simvastatin from another statin between August 2003 and March 2006, not receiving other lipid lowering medications in the 12 months before or after initiating statin therapy	N=277 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction in LDL-C from baseline	Primary: Patients switched to rosuvastatin experienced a significant reduction in LDL-C from baseline compared to simvastatin-treated patients (18.5% vs 5.8%; P<0.05). LDL-C reduction of >25% was achieved by a significantly greater percentage of patients switched to rosuvastatin therapy than those switched to simvastatin therapy (44% vs 29%; P<0.05). Patients switched from atorvastatin to rosuvastatin experienced a significantly greater reduction in LDL-C from baseline compared to those switched to simvastatin therapy (14.6% vs 4.6%; P<0.05).
Ballantyne et al.[66] (2007)	MC, OL, PG, RCT	N=469	Primary: Percentage of	Primary: Significantly greater proportion of patients randomized to the combination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
EXPLORER Rosuvastatin 40 mg daily for 6 weeks vs ezetimibe 10 mg, in addition to rosuvastatin 40 mg daily, separate entities, for 6 weeks	Patients ≥18 years of age with primary hypercholesterolemia and CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score >20%), and mean LDL-C between 160 mg/dL and 250 mg/dL with the two last measurements within 15% of each other, and TG <400 mg/dL	6 weeks	patients achieving the ATP III LDL-C goal (<100 mg/dL) at 6 weeks Secondary: Change from baseline in LDL-C, TC, non–HDL-C, TG, LDL:HDL cholesterol, TC:HDL, non-HDL/HDL, apo B, CRP, HDL, apo AI, adverse effects	therapy achieved their ATP III LDL-C goal compared to the monotherapy group (94% vs 79.1%; P<0.001). Secondary: Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL-C compared to the monotherapy group (70% vs 57%; P<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC compared to the monotherapy group (51% vs 42%; P<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non–HDL-C compared to the monotherapy group (65% vs 52%; P<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TG compared to the monotherapy group (35% vs 25%; P<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in LDL:HDL cholesterol compared to the monotherapy group (72% vs 60%; P<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in TC:HDL cholesterol compared to the monotherapy group (56% vs 45%; P<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in non-HDL/HDL cholesterol compared to the monotherapy group (67% vs 55%; P<0.001). Patients on the combination therapy experienced a significantly greater reduction from baseline in apo B compared to the monotherapy group (56% vs 45%; P<0.001). Patients on the combination therapy experienced a significantly greater

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reduction from baseline in CRP compared to the monotherapy group (46% vs 29%; P<0.001). There was no statistically significant difference in HDL-C increase (P=0.151) or apo AI reduction (P=0.202) between the combination therapy and rosuvastatin monotherapy groups. The frequency and types of adverse events were similar across the combination and monotherapy groups (31.5% and 33.5%, respectively).
McKenney et al.[70] (2007) COMPELL Rosuvastatin 10 mg for the first 4 weeks, titrated up to 20 mg on weeks 5-8, and 40 mg on weeks 9-12 vs atorvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to niacin SR 500 mg for the first 4 weeks, separate entities, titrated up to 1,000 mg on weeks 5-8, and 2,000 mg on weeks 9-12 vs	MC, OL, PG, RCT Adult patients ≥21 years of age with hypercholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with two consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL	N=292 12 weeks	Primary: LDL-C level at week 12 Secondary: HDL-C level at week 12, non–HDL-C, TG, Lp(a), apo B, side effects	Primary: Patients randomized to atorvastatin/niacin SR, rosuvastatin/niacin SR, simvastatin/ezetimibe, and rosuvastatin therapies experienced similar reductions in LDL-C from baseline at week 12 of the study (56%, 51%, 57%, 53%, respectively; P=0.093). Secondary: Patients randomized to atorvastatin/niacin SR experienced a statistically significant increase in HDL-C from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (22%, 10%, and 7%, respectively; P≤0.05). There was no significant difference in the reduction of non–HDL-C from baseline among treatment groups (P=0.053). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in TG from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin groups (47%, 33%, and 25%, respectively; P≤0.05). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in Lp(a) from baseline at week 12 of the study compared to the simvastatin/ezetimibe and rosuvastatin 20 mg groups (–14%, +7%, and +18%, respectively; P≤0.05). Patients randomized to atorvastatin/niacin SR experienced a statistically significant reduction in apo B from baseline at week 12 of the study compared to the rosuvastatin group (43% vs 39%, respectively; P≤0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 20 mg for the first 8 weeks, titrated up to 40 mg on weeks 9-12 in addition to ezetimibe 10 mg, separate entities, for 12 weeks vs rosuvastatin 10 mg for the first 8 weeks, titrated up to 20 mg on weeks 9-12, in addition to niacin SR 500 mg, separate entities, for the first 4 weeks, titrated up to 1,000 mg on weeks 5-12				Side effects were similar across treatment groups. There were no cases of myopathy or hepatotoxicity reported during the study period.
Nicholls et al.[179] (2010) VOYAGER Rosuvastatin (variable doses) vs atorvastatin (variable doses) vs	MA Patients with hypercholesterolemia	N=32,258 (37 trials) Variable duration	Primary: Impact of increasing dose on lowering LDL-C, TG, non-HDL-C, and apo B	Primary: Increasing doses of all agents resulted in an incremental benefit on LDL-C reduction. The incremental impact of dose doubling was comparable, with a 5% to 7% increase in LDL-C lowering. A greater percentage of patients achieved LDL-C treatment goals using increasing doses of all agents, as well as in patients with lower cholesterol levels at baseline. Increasing doses of all agents resulted in an incremental benefit on TG reduction. The incremental impact of dose doubling was comparable, with a 2% to 4% increase in TG lowering. Increasing doses of all agents resulted in an incremental benefit on non-HDL-C reduction. The incremental impact of dose doubling was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin (variable doses)				comparable, with a 4% to 6% increase in non-HDL-C lowering. Increasing doses of all agents resulted in an incremental benefit on apo B reduction. The incremental impact of dose doubling was comparable, with a 4% to 6% increase in apo B lowering. Increasing statin dose was not associated with an increase in withdrawal rates due to adverse events.
Wlodarczyk et al.[172] (2008) Rosuvastatin (5, 10, 20, and 40 mg) vs atorvastatin (10, 20, 40, and 80 mg	MA Patients with dyslipidemia	N=19,621 (25 trials) Variable duration	Primary: Percentage of LDL-C reduction, risk (myalgia, increased ALT >3 times the upper limit of normal, CK >10 times the upper limit of normal [ULN], percent change in glomerular filtration rate, deaths, serious adverse events), and rates of withdrawal	Primary: Treatment with rosuvastatin (1:1 dose ratio) led to greater reductions in LDL-C compared to atorvastatin (-8.52%; 95% CI, -9.23 to -7.81). Treatment with rosuvastatin (1:2 dose ratio) led to greater reductions in LDL-C compared to atorvastatin (-3.24%; 95% CI, -4.10 to -2.38). There was no significant difference in LDL-C when rosuvastatin was compared with a 4 times higher atorvastatin dose (1.12%; 95% CI -0.24 to 2.48). The percentage reduction in LDL-C was 41.0% to 56.0% for rosuvastatin 5 mg and 40 mg doses, respectively. The percentage reduction in LDL-C was 37.2% to 51.3% for atorvastatin 10 mg and 80 mg doses, respectively. There was no significant difference in the incidence of myalgia, serious adverse events, ALT >3 times the ULN, CK >10 times the ULN, percent change in GFR, or withdrawal rates due to adverse events with rosuvastatin and atorvastatin.
Meredith et al.[41] (2007) Simvastatin 20 mg once daily vs simvastatin 80 mg once daily	DB, PG, RCT Patients who had undergone elective coronary angiography, had stable CAD, and an HsCRP >3 mg/L	N=107 16 weeks	Primary: Change in HsCRP from baseline Secondary: Change in LDL-C, TC, TG from baseline	Primary: There was no statistically significant difference between simvastatin 20 and 80 mg groups in terms of change in HsCRP from baseline (P=0.82). Secondary: Simvastatin, regardless of dose, was more effective than placebo in LDL-C reduction from baseline (P<0.001). Simvastatin, regardless of dose, was more effective than placebo in HsCRP reduction from baseline (P=0.007).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo once daily				Simvastatin, regardless of dose, was more effective than placebo in TC reduction from baseline (P<0.001). Simvastatin, regardless of dose, was more effective than placebo in triglyceride reduction from baseline (P=0.01).
Rogers et al.[53] (2007) Simvastatin 10, 20, 40, or 80 mg daily vs atorvastatin 10, 20, 40, or 80 mg daily	MA Randomized, comparative studies comparing atorvastatin with simvastatin in patients >18 years of age with elevated levels of serum TC and LDL-C	N=8,320 (18 trials) Up to 12 weeks	Primary: Reductions in TC, LDL-C, TG and increases in HDL-C	Primary: Simvastatin appeared to be comparable to atorvastatin in terms of TC reduction from baseline at 4 times the dose of atorvastatin (P>0.05). Simvastatin 20 mg and 40 mg were less effective at reducing LDL-C level from baseline compared to atorvastatin 40 mg and 80 mg, respectively (P<0.001). Simvastatin, dosed 40 mg to 80 mg, was comparable to atorvastatin 20 mg in terms of triglyceride reduction from baseline (P=0.22 and P=0.53, respectively). Atorvastatin, dosed 40 mg to 80 mg, was more effective in reducing triglyceride level from baseline compared to all simvastatin doses studied (P<0.001). Simvastatin 10 mg, 20 mg, and 80 mg were more effective than atorvastatin 80 mg in increasing HDL-C from baseline (P<0.05).
Ose et al.[67] (2007) Simvastatin 10 mg, 20 mg, 40 mg, or 80 mg daily for 14 weeks vs ezetimibe 10 mg daily added to simvastatin 10 mg,	DB, MC, RCT Extension of a 12-week study in patients, aged 22 to 83 years, with primary hypercholesterolemia (LDL-C between 145 mg/dL and 250 mg/dL and TG <350 mg/dL) who were randomized to ezetimibe/simvastatin	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, TC, non-HDL, CRP, LDL:HDL cholesterol ratio, TC:HDL ratio, proportion of patients reaching LDL-C target (<100 mg/dL, or <70 mg/dL)	Primary: Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared with the simvastatin monotherapy group (53.7% vs 38.8%; P<0.001). Across all doses, patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant reduction from baseline in TG, TC, non-HDL, CRP, LDL:HDL cholesterol ratio, and TC:HDL ratio compared with the simvastatin monotherapy group (P<0.001). Significantly greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <100 mg/dL,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
20 mg, 40 mg, or 80 mg daily, separate entities, for 14 weeks vs ezetimibe 10 mg once daily for 14 weeks vs placebo once daily for 14 weeks	10/10, 10/20, 10/40 or 10/80 mg combination tablet, simvastatin 10, 20, 40, or 80 mg monotherapy, ezetimibe 10 mg, or placebo			compared to the simvastatin group (79.2% vs 47.9%; P<0.001). A greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (30.4% vs 7%; P<0.001). The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin and simvastatin monotherapy groups (7.4% vs 5.5%, respectively).
Patel et al.[68] (2006) Simvastatin 20 mg, in addition to placebo for 6 weeks vs ezetimibe 10 mg, in addition to simvastatin 20 mg, separate entities, for 6 weeks	DB, MC, PG, RCT Patients 18-75 years of age with primary hypercholesterolemia and CHD (at least 3 months prior to baseline), not on lipid management therapy	N=153 6 weeks	Primary: Mean change from baseline in LDL-C level, proportion of patients who reached LDL-C target (<3 mmol/l) at 6 weeks Secondary: Change in serum cholesterol, TG, HDL	Primary: Patients on the combination therapy experienced an additional LDL-C reduction of 14.6% compared to the simvastatin monotherapy group (95% CI, 10.1 to 19.1; P<0.0001). Significantly greater proportion of patients randomized to the combination therapy achieved their LDL-C goal compared to the monotherapy group (93% vs 75%, respectively; P<0.001). Patients on combination therapy were 5.1 times more likely to reach target LDL-C levels compared to patients on simvastatin alone (95% CI, 1.8 to 15.0; P=0.003). Secondary: Patients on the combination therapy experienced an additional TC reduction of 0.69 mmol/L compared to the simvastatin group (95% CI, 0.48 to 0.90; P<0.0001). Significantly greater proportion of patients in the combination therapy group reached TC target (<4 mmol/L) compared to simvastatin group (P<0.001). Greater reduction in TG was observed in the combination therapy group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to the simvastatin group (20.4% vs 12.4%; P=0.06). There was no difference in the change of HDL level from baseline between the two groups (~6% increase in each group). There was no statistically significant difference in treatment emergent adverse events between the combination therapy and simvastatin groups (40% vs 25%; P=0.07).
Chenot et al.[69] (2007) Simvastatin 40 mg daily vs ezetimibe 10 mg daily added to simvastatin 40 mg daily, separate entities vs no lipid-lowering therapy	RCT Patients, average age 61 years, admitted for an AMI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission	N=60 7 days	Primary: Change from baseline in LDL-C at days 2, 4 and 7, and the achievement of LDL-C <70 mg/dL	Primary: Patients on the ezetimibe/simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (27%, 41%, and 51%, respectively; P<0.001). Patients on the simvastatin monotherapy experienced a statistically significant LDL-C reduction from baseline on days 2, 4, and 7 (15%, 27%, and 25%, respectively; P<0.001). There was no statistically significant change from baseline in LDL-C in the no lipid-lowering therapy group (P≥0.09). Patients on the ezetimibe/simvastatin combination therapy achieved lower LDL-C levels compared to the simvastatin monotherapy group at day 4 (P=0.03) and day 7 (P=0.002) of the study. A greater proportion of patients randomized to the ezetimibe/simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin monotherapy group at day 4 and day 7 (45% vs 5%, and 55% vs 10%, respectively).
Gaudiani et al.[153] (2005) Simvastatin 20 mg daily for 6 weeks, followed by the addition of ezetimibe 10 mg daily for another 24	DB, MC, PG, RCT Patients 30-75 years of age with type 2 diabetes (hemoglobin A1C ≤9%), treated with a stable dose of pioglitazone (15-45 mg daily) or	N=214 30 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change from baseline in total cholesterol,	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (20.8% vs 0.3%; P<0.001). Secondary: Total cholesterol was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (14.5% vs 1.5%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks, separate entities vs simvastatin 20 mg daily for 6 weeks, titrated up to 40 mg daily for another 24 weeks, separate entities	rosiglitazone (2-8 mg daily) for at least 3 months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy)		TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI	Non–HDL-C was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (20% vs 1.7%; P<0.001). Apo B was reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (14.1% vs 1.8%; P<0.001). The ratios of LDL-C:HDL-C, TC:HDL-C, and apo B to apo AI were reduced more by the addition of ezetimibe 10 mg to simvastatin 20 mg than by doubling the dose of simvastatin 20 mg (P<0.001). The reduction in HDL-C was similar in the simvastatin 40 mg and simvastatin-ezetimibe 10/20 mg groups (P=948). The incidence of treatment-related adverse effects was lower in the simvastatin 40 mg group than in the simvastatin-ezetimibe 10/20 mg group (10% and 18.3%, respectively).
Feldman et al.[154] (2004) Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs	DB, MC, RCT Patients 18-80 years of age with CHD or CHD risk equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL, not pregnant, liver transaminase and CK ≤50% above the ULN, off all lipid-lowering agents ≥6 weeks	N=710 23 weeks	Primary: LDL-C <100 mg/dL at week 5 Secondary: LDL-C <100 mg/dL at study end	Primary: Significantly more patients on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 5, compared with patients receiving simvastatin 20 mg monotherapy (P<0.001). Secondary: Significantly more patients on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 23, compared with patients receiving simvastatin 20 mg monotherapy (P<0.001). At week 5, there was a statistically significant reduction in total cholesterol, non–HDL-C, apo B, ratios of TC:HDL-C, and LDL-C:HDL-C among patients randomized to the simvastatin-ezetimibe combination therapy, regardless of the dose, compared with patients receiving simvastatin 20 mg monotherapy (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 23 weeks, separate entities vs simvastatin 20 mg daily for 23 weeks				HDL-C was significantly increased only in the simvastatin-ezetimibe 10/20 mg group from baseline, compared with simvastatin monotherapy (P<0.05). At week 5, there was a statistically significant reduction in TG among patients randomized to the simvastatin-ezetimibe combination therapy, regardless of the dose, compared with patients receiving simvastatin 20 mg monotherapy (P<0.05). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe 10/10 mg, 10/20 mg, 10/40 mg groups (7.5%, 9.6%, 14%, and 10%, respectively).
Goldberg et al.[156] (2004) Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the ULN, no active liver disease, CK ≤1.5 times the ULN	N=887 20 weeks	Primary: Mean percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/simvastatin vs simvastatin alone Secondary: Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP, proportion of patients reaching their NCEP ATP	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant 14.8% reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (53.2% vs 38.5%; P<0.001). Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (P<0.001). Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (P<0.001). Averaged across all doses, simvastatin-ezetimibe combination resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, or <100 mg/dL at 12 weeks, compared with simvastatin (92% and 82% vs 82% and 43%, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 80 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks			III LDL-C goal of <130 mg/dL, or <100 mg/dL at 12 weeks	Averaged across all doses, simvastatin-ezetimibe combination therapy was not associated with a statistically significant change from baseline in HDL-C level, compared with simvastatin monotherapy (P=0.53). Treatment-related adverse effects were similar in the pooled simvastatin and simvastatin-ezetimibe, but were more frequent than in the ezetimibe and placebo groups (13%, 14%, 9%, and 9%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Davidson et al.[157] (2002) Simvastatin 10 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 20 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 40 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 80 mg daily, in addition to ezetimibe 10 mg daily for 12 weeks, separate entities vs simvastatin 10 mg daily for 12 weeks	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia	N=668 20 week	Primary: Mean percent change in LDL-C from baseline to the end of treatment period Secondary: Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (49.9% vs 36.1%; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with ezetimibe monotherapy (49.9% vs 18.1%; P<0.001). Patients randomized to either simvastatin-ezetimibe 10/10 mg or simvastatin 80 mg monotherapy experienced a 44% reduction in LDL-C from baseline at 12 weeks. Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks (P<0.001). Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (P<0.01). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, and apo B from baseline at 12 weeks, compared with simvastatin monotherapy (P<0.01). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a statistically significant increase from baseline in HDL-C level, compared with simvastatin monotherapy (P=0.03). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, and apo B from baseline at 12 weeks, compared with ezetimibe monotherapy (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a statistically significant increase from baseline in HDL-C level, compared with ezetimibe monotherapy (P=0.02). A significantly greater proportion of patients on simvastatin-ezetimibe therapy experienced a reduction in LDL-C >50% from baseline, compared with the simvastatin monotherapy group. Treatment-related adverse effects were similar in the pooled simvastatin and simvastatin-ezetimibe groups (72% and 69%, respectively).
Bays et al.[155] (2004) Simvastatin-ezetimibe 10 mg/10 mg daily for 12 weeks, combination product vs simvastatin-	DB, MC, RCT Patients aged 18 to 80 years with primary hypercholesterolemia, LDL-C >145 mg/dL but ≤150 mg/dL and TG ≤350 mg/dL; patients were excluded if they had an active liver disease	N=1,528 24 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period for pooled ezetimibe/simvastatin vs simvastatin or ezetimibe monotherapy Secondary:	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with simvastatin monotherapy (53% vs 39%; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with ezetimibe monotherapy (53% vs 18.9%; P<0.001). Secondary: At each corresponding dose of simvastatin, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe 10 mg/20 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/40 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/80 mg daily for 12 weeks, combination product vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs	and CK >1.5 times the ULN		Change and percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and C-reactive protein (CRP), proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, <100 mg/dL, or <70 mg/dL at 12 weeks	from baseline at 12 weeks (P<0.001). Simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 12 weeks, compared with the next highest dose of simvastatin (P<0.001). Averaged across all doses, simvastatin-ezetimibe combination resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal of <130 mg/dL, <100 mg/dL, or <70 mg/dL at 12 weeks, compared with simvastatin (92.2%, 78.6%, 38.7% vs 79.2%, 45.9%, and 7.0%, respectively; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in total cholesterol, TG, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was not associated with a statistically significant change from baseline in HDL-C level, compared with simvastatin monotherapy (P=0.607). Treatment-related adverse effects were similar in the pooled simvastatin, simvastatin-ezetimibe, and ezetimibe groups, but were more frequent than placebo (14.8%, 15.1%, 12.8%, 8.1%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				
Feldman et al.[158] (2006) Simvastatin-ezetimibe 10 mg/10 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/20 mg daily for 12 weeks, combination product vs simvastatin-ezetimibe 10 mg/40 mg daily for 12 weeks, combination product	MA Post hoc analysis of three randomized, double-blind, placebo controlled studies among patients with primary hypercholesterolemia	N=3,083 (3 trials) 28 weeks	Primary: Percent change in LDL-C, TG, non–HDL-C, apo B, and CRP from baseline, achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C, TG, non–HDL-C, apo B, and CRP from baseline at 12 weeks, compared with simvastatin monotherapy (P<0.001). These affects did not differ between the older and younger patients. Treatment with simvastatin-ezetimibe and simvastatin monotherapy resulted in comparable increases in HDL-C from baseline (8% vs 7%, respectively). Significantly more patients, in all age groups, on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12, compared with patients receiving simvastatin monotherapy (79% vs 42%; P<0.001). Significantly more patients, in all age groups, on the simvastatin-ezetimibe combination therapy, regardless of the dose, achieved an LDL-C level <70 mg/dL at week 12, compared with patients receiving simvastatin monotherapy (37% vs 6%; P<0.001). Treatment-related adverse effects were similar in simvastatin and simvastatin-ezetimibe combination therapy groups, regardless of dose used and age group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin-ezetimibe 10 mg/80 mg daily for 12 weeks, combination product vs simvastatin 10 mg daily for 12 weeks vs simvastatin 20 mg daily for 12 weeks vs simvastatin 40 mg daily for 12 weeks vs simvastatin 80 mg daily for 12 weeks vs ezetimibe 10 mg daily for 12 weeks vs placebo daily for 12 weeks				
Ballantyne et al.[159]	DB, MC, RCT	N=788	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Simvastatin-ezetimibe 10 mg/20 mg, combination product, daily for weeks 1-6, titrated to simvastatin-ezetimibe 10 mg/40 mg for weeks 7-18, titrated to simvastatin-ezetimibe 10 mg/80 mg for weeks 19-24 vs simvastatin-ezetimibe 10 mg/10 mg, combination product, daily for weeks 1-6, titrated to simvastatin-ezetimibe 10 mg/20 mg for weeks 7-12, titrated to simvastatin-ezetimibe 10 mg/40 mg for weeks 12-18, titrated to simvastatin-ezetimibe 10 mg/80 mg for weeks 19-24 vs atorvastatin 10 mg	Patients ≥18 years with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10-year risk of >20% for CHD, and with LDL cholesterol ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10-year risk of <20% for CHD, and with LDL-C ≥160 mg/dL, and no CHD or its risk equivalent with <2 risk factors and with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the ULN, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the ULN, and a hemoglobin A1C <9% in patients with diabetes	24 weeks	Mean percent change in LDL-C from baseline to end of treatment period Secondary: Percent change in LDL-C and HDL-C from baseline to the ends of the second and fourth (final) 6-week treatment periods	Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline, compared with atorvastatin monotherapy (52.4% vs 45.1%; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in HDL-C from baseline, compared with atorvastatin monotherapy (12.3% vs 6.5%; P<0.001). Secondary: At the end of treatment period 2, patients randomized to simvastatin-ezetimibe 10/20 mg and 10/40 mg experienced a significant reduction in LDL-C from baseline, compared with the atorvastatin 20 mg monotherapy group (50.2%, 54.3%, and 44.3%, respectively; P≤0.05). At the end of treatment period 2, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant increase in HDL-C from baseline, compared with the atorvastatin 20 mg monotherapy group (12.4% vs 6.9%; P≤0.05). At the end of treatment period 4, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant reduction in LDL-C from baseline, compared with the atorvastatin 80 mg monotherapy group (59.4% vs 52.5%, respectively; P≤0.05). At the end of treatment period 4, patients randomized to simvastatin-ezetimibe 10/40 mg experienced a significant increase in HDL-C from baseline, compared with the atorvastatin 80 mg monotherapy group (12.3% vs 6.5%; P≤0.05). The safety of simvastatin-ezetimibe was observed to be similar to that of atorvastatin monotherapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for weeks 1-6, titrated to atorvastatin 20 mg for weeks 7-12, titrated to atorvastatin 40 mg for weeks 12-18, titrated to atorvastatin 80 mg for weeks 19-24				
Ballantyne et al.[160] (2005) VYVA Simvastatin-ezetimibe 10 mg/10 mg daily, combination product for 6 weeks vs simvastatin-ezetimibe 10 mg/20 mg daily, combination product for 6 weeks vs simvastatin-ezetimibe 10 mg/40 mg daily, combination product for 6 weeks vs	DB, MC, PG, RCT Adult patients with hypercholesterolemia, between 18 and 79 years of age, with an LDL-C level at or above drug treatment thresholds established by NCEP ATP III, with established CHD or CHD risk equivalent with an LDL-C ≥130 mg/dL, no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD ≥10% and ≤20% with an LDL-C ≥130 mg/dL, no established CHD or CHD risk equivalent, with ≥2 risk factors conferring a 10-year risk for CHD <10%	N=1,902 10 weeks	Primary: Mean percent change from baseline in LDL-C at 6 weeks Secondary: Percent change from baseline in LDL-C at each mg-equivalent statin dose comparison, percent change from baseline in HDL-C, percentage of patients that reached NCEP ATP III LDL-C goal	Primary: Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin (53.4% vs 45.3%; P<0.001). Secondary: Simvastatin-ezetimibe 10/20 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 10 mg (50.6% vs 36.1%; P<0.001), and atorvastatin 20 mg therapy (50.6% vs 43.7%; P<0.001). Simvastatin-ezetimibe 10/40 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 40 mg (57.4% vs 48.3%; P<0.001). Simvastatin-ezetimibe 10/80 mg combination therapy was associated with a significant reduction in LDL-C from baseline at 6 weeks, compared with atorvastatin 80 mg (58.6% vs 52.9%; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in HDL-C from baseline at 6 weeks, compared with atorvastatin (7.9% vs 4.3%; P<0.001). A greater proportion of patients reached their NCEP ATP III LDL-C goal at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (89.7% vs 81.1%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin-ezetimibe 10 mg/80 mg daily, combination product for 6 weeks vs atorvastatin 10 mg daily for 6 weeks vs atorvastatin 20 mg daily for 6 weeks vs atorvastatin 40 mg daily for 6 weeks vs atorvastatin 80 mg daily for 6 weeks	with an LDL-C ≥160 mg/dL; and no established CHD or CHD risk equivalent, with ≥2 risk factors, and with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT, AST, or CK level ≤1.5 times the ULN, serum creatinine ≤1.5 mg/dL, and hemoglobin A1C <9.0% in patients with diabetes			A greater proportion of patients with a CHD or a CHD risk equivalent reached their NCEP ATP III LDL-C goals of <100 mg/dL at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (85.4% vs 70%; P<0.001). A greater proportion of patients with a CHD or a CHD risk equivalent reached their NCEP ATP III LDL-C goals of <70 mg/dL at 6 weeks with simvastatin-ezetimibe combination therapy (averaged across all doses), compared with atorvastatin therapy (45.3% vs 20.5%; P<0.001). Averaged across all doses, simvastatin-ezetimibe combination therapy was associated with a significant increase in the risk of ALT/AST elevation >3 times the ULN, compared with atorvastatin therapy (P=0.006).
Farnier et al.[161] (2007) Simvastatin-ezetimibe 10 mg/20 mg for 12 weeks, combination product vs	DB, I, MC, PG, RCT Patients ≥18 years of age with mixed hypercholesterolemia, no CHD or a CHD risk equivalent disease (except for diabetes), or 10-year CHD risk score >20% according to the	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in total cholesterol, TG, HDL, non-HDL cholesterol,	Primary: Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction in LDL-C from baseline compared with the fenofibrate monotherapy group (45.8% vs 15.7%; P<0.05). There was no significant difference between LDL-C reduction seen with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (45.8% vs 47.1%; P>0.2). Secondary: Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin-ezetimibe 10 mg/20 mg, combination product, in addition to fenofibrate 160 mg for 12 weeks vs fenofibrate 160 mg for 12 weeks vs placebo for 12 weeks	NCEP ATP III criteria		LDL:HDL cholesterol, TC:HDL, non-HDL/HDL, apo B	from baseline in non-HDL cholesterol, TG, and apo B compared with the other treatment groups (P<0.01). There was no significant difference between total cholesterol reduction seen with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (38.7% vs 35.4%; P>0.05). Simvastatin-ezetimibe/fenofibrate group exhibited significant increase from baseline in HDL cholesterol compared with the simvastatin-ezetimibe group (18.7% vs 9.3%; P<0.01). Simvastatin-ezetimibe/fenofibrate group exhibited significant reduction from baseline in LDL:HDL cholesterol, TC:HDL compared with the simvastatin-ezetimibe group (P=0.03). There was no significant difference between the percentage of patients able to reach their LDL-C goal with the simvastatin-ezetimibe/fenofibrate therapy and simvastatin-ezetimibe therapy (88.5% vs 92.9%).
Hall et al.[180] (2009) SPACE ROCKET Simvastatin 40 mg once daily vs rosuvastatin 10 mg once daily	RCT, OL, MC, PG Patients within 2 weeks of a myocardial infarction (MI) with at least one of the following: ischemic symptoms, development of pathological Q waves on the ECG, ECG changes indicative of ischemia or those requiring secondary prevention with a statin	N=1,263 3 months	Primary: Achievement of European Society of Cardiology 2003 (ESC-03) lipid targets [LDL-C <97 mg/dl or TC <174mg/dl Secondary: Achievement of NCEP ATP III target (LDL-C <100 mg/dl), National Service Framework (NSF) targets (LDL-C <116 mg/dl or TC <193 mg/dl),	Primary: After 3 months, 77.6% of patients receiving simvastatin and 79.9% of patients receiving rosuvastatin achieved at least one of the ESC-03 lipid targets. There was no difference between the treatment groups (OR, 1.162; 95% CI, 0.882–1.531; P=0.286). Secondary: After 3 months, 75.2% of patients receiving simvastatin and 77.6% of patients receiving rosuvastatin achieved the NCEP ATP III LDL-C target. There was no difference between the treatment groups (P=0.302). After 3 months, 86.7% of patients receiving simvastatin and 89.3% of patients receiving rosuvastatin achieved at least one of the NSF lipid targets. There was no difference between the treatment groups (P=0.147). After 3 months, 57.5% of patients receiving simvastatin and 61.9% of patients receiving rosuvastatin achieved at least one of the JBS-2 targets. There was no difference between the treatment groups (P=0.087).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Second Joint British Societies (JBS-2) targets (LDL-C <77 mg/dl or TC <155 mg/dl), lipid parameters	There was no difference between the treatment groups in HDL-C and TG levels. TC and LDL-C levels were lower with rosuvastatin than simvastatin (P=0.005 and P=0.009, respectively).
Primary Prevention of Coronary Heart Disease Events				
Colhoun et al.[71] (2004) CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Patients between 40 and 75 years of age with type 2 diabetes without a history of CHD, LDL-C level ≤160 mg/dL, TG ≤600 mg/dL and at least one other CHD risk factor	N=2,838 3.9 years	Primary: Major cardiovascular events (CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) Secondary: All-cause mortality, acute hospital-verified cardiovascular end point (major CVD events, angina, transient ischemic attack, peripheral vascular disease requiring hospitalization or surgery), reduction in coronary revascularization, lipid reduction	Primary: Atorvastatin treatment led to a 37% reduction in the relative risk of the primary end point compared to control (95% CI, 17 to 52; P=0.001). Secondary: Atorvastatin treatment led to a 27% reduction in the relative risk of all-cause mortality compared to control (95% CI, 1 to 48; P=0.059). Atorvastatin treatment led to a 32% reduction in the relative risk of any cardiovascular end point compared to control (95% CI, 15 to 45; P=0.001). Atorvastatin therapy was associated with a significant reduction in stroke compared to control (1.5% vs 2.8%; HR, 0.52; 95% CI, 0.31 to 0.89). Atorvastatin therapy was not associated with a significant reduction in coronary revascularization compared to control (HR, 0.69; 95% CI, 0.41 to 1.16). Atorvastatin treatment was associated with a 40% reduction in the LDL-C levels from baseline compared with control (P<0.0001). Atorvastatin treatment was associated with a 26% reduction in the TC levels from baseline compared with control (P<0.0001). Atorvastatin treatment was associated with a 1% increase in the HDL-C level from baseline compared with control (P=0.0002). Atorvastatin treatment was associated with a 36% reduction in non–HDL-C level from baseline compared with control (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Atorvastatin treatment was associated with a 19% reduction in the TG level from baseline compared with control (P<0.0001). Atorvastatin treatment was associated with a 23% reduction in apo B level from baseline compared with control (P<0.0001). The frequency of adverse events was similar in all study groups.
Neil et al.[72] (2006) CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Post hoc analysis of CARDS study, evaluating safety and efficacy of atorvastatin in patients ≥65 years of age (see above)	N=2,838 3.9 years	Primary: Major cardiovascular events (acute CHD death, nonfatal MI, including silent MI on annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) among patients ≥65 and <65 years of age Secondary: All-cause mortality, acute hospital-verified cardiovascular end point (major CVD events, angina, transient ischemic attack, peripheral vascular disease requiring hospitalization or surgery) among	Primary: Atorvastatin treatment led to a 38% reduction in the relative risk of the primary end point in patients ≥65 years of age (95% CI, 8 to 58; absolute risk reduction [ARR], 3.9%, P=0.017). Consequently, 21 patients would need to be treated for 4 years to prevent one major cardiovascular event. Atorvastatin treatment led to a 37% reduction in the relative risk of the primary end point in patients <65 years of age (95% CI, 7 to 57; ARR, 2.7%; P=0.019). Consequently, 33 patients would need to be treated for 4 years to prevent one major cardiovascular event. Secondary: There was no statistically significant effect on all-cause mortality in either the <65 (P=0.98) or the ≥65 year old population (P=0.245). Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the LDL-C levels among both the younger and the older patients (38% and 41%, respectively; P<0.001). Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the TC levels among both the younger and the older patients (26% and 27%, respectively; P<0.001). Compared to placebo, atorvastatin treatment led to a statistically significant reduction in the triglyceride level among both the younger and the older patients (P<0.001). The frequency of adverse events was similar in all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			patients ≥65 and <65 years of age	
Hitman et al.[73] (2007) CARDS Atorvastatin 10 mg daily after a 6-week placebo run-in period vs placebo daily after a 6-week placebo run-in period	DB, MC, RCT Subanalysis of CARDS study, evaluating stroke prevention with atorvastatin therapy (see above)	N=2,838 3.9 years	Primary: Fatal or nonfatal stroke, type of stroke, risk factors for stroke	Primary: Atorvastatin therapy was associated with a significant 48% reduction in stroke compared to control (1.5% vs 2.5%; HR, 0.52; 95% CI, 0.31 to 0.89; P=0.016). Atorvastatin therapy was associated with a significant 50% reduction in non-hemorrhagic stroke compared to control (1.1% vs 2.2%; HR, 0.50; 95% CI, 0.27 to 0.91; P=0.024). Atorvastatin therapy was associated with a significant 42% reduction in stroke or transient ischemic attacks compared to control (2.1% vs 3.6%; HR, 0.58; 95% CI, 0.37 to 0.92; P=0.019). Independent risk factors predicting stroke were age (HR, 2.3; P<0.001), microalbuminuria (HR, 2.0; P=0.007), and glycemic control (HR, 2.7; P=0.007). Women were at a lower risk for stroke than men (HR, 0.3; P=0.004).
Sever et al.[74] (2003) ASCOT-LLA Atorvastatin 10 mg daily, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively)	DB, MC, RCT Patients between 40 and 79 years of age with either untreated or treated hypertension, TC ≤6.5 mmol/L, and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardio-vascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes	N=10,305 3.3 years	Primary: Combined end point of nonfatal MI, and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal heart failure, fatal and nonfatal stroke, total coronary end	Primary: Compared to placebo, atorvastatin 10 mg daily was associated with a 36% reduction in the primary end point (HR, 0.64; 95% CI, 0.50 to 0.83; P=0.0005). Secondary: Compared to placebo, atorvastatin 10 mg daily was associated with a 38% reduction in the primary end point, excluding silent MIs (HR, 0.62; 95% CI, 0.47 to 0.81; P=0.0005). Atorvastatin 10 mg daily was not associated with a significant reduction in all-cause mortality (P=0.1649), cardiovascular mortality (P=0.5066), or fatal and nonfatal heart failure (P=0.5794) compared with control. Compared to placebo, atorvastatin 10 mg daily was associated with a 27% reduction in the risk for fatal and nonfatal strokes (HR, 0.73; 95% CI, 0.56 to 0.96; P=0.0236).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively)	type 2, PAD, previous stroke or transient ischemic attack, age >55 years, microalbuminuria or proteinuria, male sex, smoking, ratio of plasma TC to HDL-C of >6, or family history of CHD		points, and total cardiovascular events and procedures	Compared to placebo, atorvastatin 10 mg daily was associated with a 29% reduction in the risk for total coronary events (HR, 0.71; 95% CI, 0.59 to 0.86; P=0.005). Compared to placebo, atorvastatin 10 mg daily was associated with a 21% reduction in the risk for total cardiovascular events and procedures (HR, 0.79; 95% CI, 0.69 to 0.90; P=0.0005).
Sever et al.[75] (2005) ASCOT-LLA Atorvastatin 10 mg daily, in addition to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively) vs placebo, in addition	DB, MC, RCT A two-year extension of the ASCOT-LLA trial (see above)	N=10,305 5.5 years	Primary: Combined end point of nonfatal MI, and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, total coronary end points, and total cardiovascular events	Primary: Compared to placebo, atorvastatin 10 mg daily was associated with a 36% reduction in the primary end point (HR, 0.64; 95% CI, 0.53 to 0.78; P≤0.0001). Secondary: Compared to placebo, atorvastatin 10 mg daily was associated with a 19% reduction in the risk for total cardiovascular events and procedures (HR, 0.81; 95% CI, 0.73 to 0.89; P≤0.0001). Compared to placebo, atorvastatin 10 mg daily was associated with a 27% reduction in the risk for total coronary events (HR, 0.73; 95% CI, 0.63 to 0.85; P≤0.0001). Compared to placebo, atorvastatin 10 mg daily was associated with a 37% reduction in the primary end point, excluding silent MIs (HR, 0.63; 95% CI, 0.51 to 0.77; P≤0.0001). Compared to placebo, atorvastatin 10 mg daily was associated with a 23% reduction in the risk for fatal and nonfatal strokes (HR, 0.77; 95% CI, 0.63 to 0.95; P=0.0127).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach systolic and diastolic blood pressure goals of <140 mm Hg and 90 mm Hg, respectively)				Compared to placebo, atorvastatin 10 mg daily was associated with a 15% reduction in the risk for all-cause mortality (HR, 0.85; 95% CI, 0.74 to 0.98; P=0.0219). Atorvastatin 10 mg daily was not associated with a significant reduction in cardiovascular mortality (P=0.1281), or fatal and nonfatal heart failure (P=0.9809) compared with control.
Winkler et al.[76] (2007) Fluvastatin 20 mg, 40 mg, and 80 mg (pooled group) vs placebo	MA Double-blind, randomized, placebo-controlled trials assessing ≥6 weeks of fluvastatin therapy in dyslipidemic patients with and without metabolic syndrome	N=7,043 (30 trials) ≥6 weeks	Primary: Major adverse cardiovascular events (MACEs) defined as CVD-related death, nonfatal MI, and cardiac revascularization, LDL-C, HDL-C, TC, TG, non–HDL-C, apo B	Primary: Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of any MACE compared to placebo (16% vs 22%; HR, 0.728; 95% CI, 0.6 to 0.9; P=0.001). The difference in the incidence of MACE between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.083). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death compared to placebo (3% vs 4.9%; HR, 0.62; 95% CI, 0.4 to 0.95; P=0.03). The difference in the incidence of cardiovascular death between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.478). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular intervention compared to placebo (12% vs 16%; HR, 0.75; 95% CI, 0.59 to 0.93; P=0.011). The difference in the incidence of cardiovascular intervention between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.125). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death or nonfatal MI compared to placebo (6.6% vs 9.9%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				HR, 0.65; 95% CI, 0.48 to 0.87; P=0.005). The difference in the incidence of cardiovascular death or nonfatal MI between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.288). There was no statistically significant difference in the incidence of nonfatal MI, all-cause mortality, or non-cardiovascular-related death between pooled fluvastatin- and placebo-treated patients whether or not they had the metabolic syndrome (P>0.05). In all patients, pooled fluvastatin was associated with a significant reduction from baseline in LDL-C, TC, TG, non–HDL-C, and apo B compared to placebo (P<0.001). Patients with and without the metabolic syndrome taking fluvastatin experienced similar benefits in terms of LDL-C, TC, non–HDL-C, and apo B reduction from baseline. Patients with the metabolic syndrome experienced a greater increase in HDL-C and a greater reduction in TG from baseline compared to patients without the metabolic syndrome (P<0.01).
Schouten et al.[187] (2009) DECREASE III Fluvastatin XL 80 mg once daily prior to surgery vs placebo Patients in both groups also received β-blocker therapy prior to surgery	RCT, DB, PC Patients ≥40 years of age who were scheduled for noncardiac vascular surgery (abdominal aortic aneurysm repair, distal aortoiliac reconstruction, lower-limb arterial reconstruction, or carotid-artery endarterectomy) who were statin naïve	N=497 ≥30 days post-surgery	Primary: Occurrence of myocardial ischemia Secondary: Composite of death from cardiovascular causes and nonfatal myocardial infarction	Primary: Myocardial ischemia occurred in 10.8% of patients in the fluvastatin XL group within 30 days after surgery compared to 19.0% of patients in the placebo group (HR, 0.55; 95% CI, 0.34 to 0.88; P=0.01). The number of patients who would need to be treated to prevent 1 patient from having myocardial ischemia was 12. Secondary: The composite of death from cardiovascular causes or nonfatal myocardial infarction occurred in 4.8% of patients receiving fluvastatin XL compared to 10.1% of patients receiving placebo (HR, 0.47; 95% CI, 0.24 to 0.94; P=0.03). The number of patients who would need to be treated to prevent the composite end point of death from cardiovascular causes or nonfatal myocardial infarction in 1 patient was 19.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Downs et al.[77] (1998) AFCAPS/ TexCAPS Lovastatin 20 to 40 mg once daily vs placebo once daily	DB, MC, PC, RCT Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years on a low-saturated fat, low-cholesterol diet, with TC 180-264 mg/dL, LDL-C 130-190 mg/dL, HDL ≤45 mg/dL for men or ≤47 mg/dL for women and TG ≤400 mg/dL; without a prior history of MI, angina, claudication, cerebrovascular accident, or transient ischemic attack; patients with LDL-C between 125-129 mg/dL were included when the ratio of TC to HDL was >6	N=6,605 5.2 years	Primary First acute major coronary event, defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death during at least 5 years of follow-up without clinical evidence of atherosclerotic cardiovascular disease Secondary Fatal or nonfatal coronary revascularization procedure, unstable angina, fatal or nonfatal MI, fatal or nonfatal cardiovascular events, fatal or nonfatal coronary events, cardiovascular mortality and CHD mortality, total mortality, fatal and nonfatal cancer, safety and discontinuation rates	Primary After an average follow-up of 5.2 years, lovastatin-treated patients experienced a 37% lower incidence of the first acute major coronary event than patients receiving placebo (95% CI, 0.50 to 0.79; P<0.001). Secondary Lovastatin-treated patients had 33% reduction in revascularization (95% CI, 0.52 to 0.85; P=0.001), 32% reduction in unstable angina (95% CI, 0.49 to 0.95; P=0.02), 40% reduction in the incidence of fatal or nonfatal MI (95% CI, 0.43 to 0.83; P=0.002), 25% reduction in fatal or nonfatal cardiovascular events (95% CI, 0.62 to 0.91; P=0.003), 25% reduction in fatal or nonfatal coronary events (95% CI, 0.61 to 0.92; P=0.006) compared to placebo. There were too few events to perform survival analysis on cardiovascular mortality and CHD mortality events based on prespecified criteria (1.0% in lovastatin group vs 1.4% in placebo group and 0.6% in lovastatin group vs 0.9% in lovastatin group, respectively). The overall mortality rate and fatal and nonfatal cancer rates were similar in the lovastatin and placebo groups. Discontinuation rates due to adverse events were 13.6% in the lovastatin group and 13.8% in the placebo group. Both treatment groups had similar rates of serious adverse events (34.2% in lovastatin group vs 34.1% in placebo group).
The Pravastatin Multinational Study	DB, MC, PC, RCT	N=1,062	Primary: Lipid levels at 13	Primary: At week 13, when compared to placebo, pravastatin treatment was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Group for Cardiac Risk Patients (PMS-CRP)[78] (1993) Pravastatin 20 to 40 daily vs placebo daily	Men and postmenopausal or surgically sterile women (mean of 55 years of age)	26 weeks	and 26 weeks and occurrence of cardiovascular events	associated with significant reductions in LDL-C (26%), TC (19%), and TG (12%) and significant elevations in HDL-C (7%) (P<0.001). Throughout the 26 weeks, there were no differences in the total incidence of clinical adverse events between the pravastatin and placebo groups. No MIs or cerebral infarctions occurred in the pravastatin group, and a total of 6 MIs and 3 cerebral infarctions occurred in the placebo group.
The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group[79] (2002) ALLHAT-LLT Pravastatin 40 mg daily vs usual care Vigorous cholesterol-lowering therapy in the usual care group was discouraged.	MC, OL, RCT Patients aged ≥55 years, with stage 1 or stage 2 hypertension, at least 1 additional CHD risk factor, previously enrolled in the ALLHAT study, fasting LDL-C 120-189 mg/dL for patients with no known CHD or 100-129 mg/dL for patients with known CHD, fasting TG <350 mg/dL	N=10,355 Mean 4.8 years (maximum 7.8 years)	Primary: All-cause mortality Secondary: Composite of fatal CHD or nonfatal MI, cause-specific mortality, total and site-specific cancers	Primary: All-cause mortality did not differ significantly between treatment groups (RR, 0.99; 95% CI, 0.89 to 1.11; P=0.88). Secondary: Rates of CHD (fatal CHD plus nonfatal MI) and stroke were slightly lower in the pravastatin group compared to the usual care group (RR, 0.91; 95% CI, 0.79 to 1.04; P=0.16). There were 209 total strokes in the pravastatin group and 231 in the usual care group (RR, 0.91; 95% CI, 0.75 to 1.09; P=0.31). Heart failure rates were similar in the pravastatin and usual care groups (RR, 0.99; 95% CI, 0.83 to 1.18; P=0.89). The 6-year cancer rates were similar in both groups (RR, 1.03; 95% CI, 0.89 to 1.19; P=0.66).
Nakamura et al.[80] (2006) MEGA	OL, PRO, R Men and post-menopausal women aged 40-70 years	N=8,214 Mean 5.2 years	Primary: CHD occurrence, sudden cardiac deaths, MIs, coronary	Primary: Pravastatin therapy was associated with a reduced incidence of CHD compared to the control (3.3% vs 5%; HR, 0.67; 95% CI, 0.49 to 0.91; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pravastatin 10-20 mg daily in addition to the NCEP step I diet vs NCEP step I diet	weighing ≥40 kg, with hypercholesterolemia, without a history of CHD or familial hypercholesterolemia		revascularization Secondary: CHD and cerebral infarction, all cardiovascular events, strokes, all-cause mortality	There was no statistically significant difference between the groups in either the incidence of sudden cardiac deaths or anginal episodes (P>0.05). Secondary: Pravastatin therapy was associated with a reduced incidence of MIs compared to the control (0.9% vs 1.6%; HR, 0.52; 95% CI, 0.29 to 0.94; P=0.03). Pravastatin therapy was associated with a reduced incidence of coronary revascularizations compared to the control (2% vs 3.2%; HR, 0.60; 95% CI, 0.41 to 0.89; P=0.01). Secondary: Pravastatin therapy was associated with a reduced incidence of CHD and cerebral infarctions compared to the control (5% vs 7.1%; HR, 0.70; 95% CI, 0.54 to 0.90; P=0.005). Pravastatin therapy was associated with a reduced incidence of all cardiovascular events compared to the control (6.4% vs 8.5%; HR, 0.74; 95% CI, 0.59 to 0.94; P=0.01). There was no statistically significant difference between the groups in either all-cause mortality or the incidence of strokes (P>0.05).
Shepherd et al.[81] (1995) WOSCOPS Pravastatin 40 mg daily vs placebo daily	DB, PC Men 45 to 64 years of age (mean of 55 years of age)	N=6,595 4.9 years	Primary: Occurrence of nonfatal MI or death from CHD as a first event Secondary: Occurrence of death from CHD and nonfatal MI	Primary: When compared to placebo, pravastatin produced a 31% reduction in the risk of the combined primary end point of definite nonfatal MI and death from CHD (95% CI, 17% to 43%; P<0.001). The absolute difference in the risk at five years was 2.4%. Secondary: The reduction in the risk of nonfatal MI was significant whether the definite cases of MI were considered alone or in combination with suspected cases (P≤0.001). In the analysis of both definite and suspected cases of death from CHD, there was a significant risk reduction of 33% with treatment (95% CI, 1% to 55%; P=0.042), but not in the analysis of definite cases alone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				When the effect of pravastatin treatment on death from all cardiovascular causes was analyzed, a 32% risk reduction was observed (95% CI, 3% to 53%; P=0.033). Additionally, pravastatin treatment was associated with a 31% reduction in the frequency of coronary angiography (95% CI, 10% to 47%; P=0.007) and a 37% reduction in the frequency of revascularization procedures (95% CI, 11% to 56%; P=0.009).
Ford et al.[82] (2007) WOSCOPS Pravastatin 40 mg daily for 5 years, with follow-up for subsequent 10 years vs placebo daily for 5 years, with follow-up for subsequent 10 years	DB, RCT Extension of the WOSCOPS study. Male patients, 45 to 64 years of age, with hypercholesterolemia without a history of previous MI, two determinations of LDL-C level ≥155 mg/dL, with at least 1 value that was ≥174 mg/dL and 1 value that was ≤232 mg/dL	N=6,595 15 years of total follow-up	Primary: Mortality from CHD or nonfatal MI, CHD, cardiovascular causes, all-cause mortality	Primary: Pravastatin treatment led to a statistically significant reduction in the risk of death from CHD or nonfatal MI compared to placebo over a 15-year period (11.8% vs 15.5%; HR, 0.73; 95% CI, 0.63 to 0.83; P<0.001). Pravastatin treatment led to a statistically significant reduction in the risk of death from all causes compared to placebo over a 15-year period (18.7% vs 20.5%; HR, 0.88; 95% CI, 0.79 to 0.99; P=0.03). Pravastatin treatment led to a statistically significant reduction in the risk of death from cardiovascular causes compared to placebo over a 15-year period (7.6% vs 9.0%; HR, 0.81; 95% CI, 0.68 to 0.96; P=0.01). Pravastatin treatment led to a statistically significant reduction in the risk of death from CHD compared to placebo over a 15-year period (5.1% vs 6.3%; HR, 0.78; 95% CI, 0.64 to 0.96; P=0.02). Pravastatin treatment was associated with a small increase in the risk of death from stroke compared to placebo over a 15-year period (1.6% vs 1.1%; HR, 1.37; 95% CI, 0.90 to 2.09; P=0.14).
Asselbergs et al.[83] (2004) Pravastatin 40 mg once daily and fosinopril 20 mg once daily	DB, PC, RCT Patients aged 28-75 years with persistent microalbuminuria, blood pressure <160/100 mm Hg (not on antihypertensive	N=864 46 months	Primary: Combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity (nonfatal	Primary: Pravastatin therapy was associated with a 13% reduction in the risk of the primary end point compared to placebo (4.8% vs 5.6%; P=0.649). The incidence of non-cardiovascular mortality was 2.1% in the pravastatin group compared to 1.9% in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo two matching tablets once daily	medications), TC level <8.0 mmol/L, or <5.0 mmol/L in case of previous MI, and no use of lipid-lowering medication		or myocardial ischemia, heart failure, peripheral vascular disease and/or cerebrovascular accident)	
Ridker et al.[177] (2008) JUPITER Rosuvastatin 20 mg daily vs placebo	RCT, MC, DB Men ≥50 years of age and women ≥60 years of age (who did not have cardiovascular disease) with LDL-C <130 mg/dl, TG <500 mg/dl, and high-sensitivity C-reactive protein ≥2.0 mg/l	N=17,802 Median follow-up 1.9 years; maximal follow-up 5 years	Primary: Occurrence of a first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization procedure, or death from cardiovascular causes Secondary: Components of the primary end point individually and death from any cause	Primary: The trial was stopped after a median follow-up of 1.9 years. At that time, 142 first major cardiovascular events occurred in the rosuvastatin group and 251 events occurred in the placebo group (HR, 0.56; 95% CI, 0.46 to 0.69; P<0.00001). The number of patients who would need to be treated with rosuvastatin for 2 years to prevent the occurrence of one primary end point is 95, and the number needed to treat for 4 years is 31. Secondary: Rosuvastatin was associated with a significant reduction in the rate of fatal or nonfatal myocardial infarction (HR, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), fatal or nonfatal stroke (HR, 0.52; 95% CI, 0.34 to 0.79; P=0.002), arterial revascularization or unstable angina (HR, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), the combination of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (HR, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and death from any cause (HR, 0.80; 95% CI, 0.67 to 0.97; P=0.02) compared to placebo.
Heart Protection Study (HPS) Group[84] (2003) MRC/BHF Simvastatin 40 mg once daily	DB, MC, PC, RCT Patients between the ages of 40-80 years, with a history of CHD, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and >65	N=20,536 5 years	Primary: Incidence of first nonfatal MI or coronary death, fatal or nonfatal stroke, revascularization procedures, first occurrence of major coronary	Primary: Simvastatin treatment was associated with a 27% reduction in the incidence of first nonfatal MI or coronary death following randomization (95% CI, 21 to 33; P<0.0001) compared to placebo. Among diabetic patients, a 27% reduction in the incidence of first nonfatal MI or coronary death was observed with simvastatin therapy compared with placebo (95% CI, 19 to 34%; P<0.0001). Simvastatin treatment was associated with a significant 25% reduction in the incidence of first nonfatal or fatal strokes following randomization

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo once daily	years), with TC >135 mg/dL		events, strokes, and revascularizations	(95% CI, 15 to 34; P<0.0001) compared to placebo. Simvastatin treatment was associated with a significant 26% reduction in the incidence of fatal strokes following randomization (95% CI, 14 to 36; P=0.0002) compared to placebo. Among diabetic patients, a 24% reduction in the incidence of fatal strokes was observed with simvastatin therapy compared to placebo (95% CI, 6 to 39; P=0.01). Simvastatin treatment was associated with a 24% proportional reduction in the incidence of first revascularization procedure following randomization compared with placebo (95% CI, 17 to 30; P<0.0001). Among diabetic patients, a 17% reduction in the incidence of first revascularization procedure was observed with simvastatin therapy compared to placebo (95% CI, 3 to 30; P=0.02). Simvastatin treatment was associated with a 24% reduction in the first occurrence of major coronary events, strokes, and revascularizations compared to placebo (95% CI, 19 to 28; P<0.0001). Among diabetic patients, a 22% reduction in the incidence of first occurrence of major coronary events, strokes, and revascularizations was observed with simvastatin therapy compared to placebo (95% CI, 13 to 30; P<0.0001).
HPS Collaborative Group[85] (2007) Simvastatin 40 mg once daily vs placebo once daily	DB, MC, RCT Patients between the ages of 40-80 years, with a history of CHD, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and ≥65 years), with TC	N=20,536 5 years	Primary: The first major coronary event (nonfatal MI or coronary death), and first major vascular event (major coronary event, stroke or revascularization)	Primary: In the overall study sample, simvastatin resulted in a significant 24% reduction in the first occurrence of a major vascular event, compared to placebo (19.8% vs 25.2%; P<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant 22% reduction in the first occurrence of a major vascular event, compared to placebo (26.4% vs 32.7%; P<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant 25% reduction in the first occurrence of a major vascular event,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	≥135 mg/dL			compared to placebo (16.5% vs 21.5%; P<0.0001). The difference in the reduction of the risk of major vascular events with statin therapy between the PAD and non-PAD groups was not statistically significant (P=0.05). In the overall study sample, simvastatin resulted in a significant 27% reduction in the first occurrence of a major coronary event, compared to placebo (8.7% vs 11.8%; P<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of a major coronary event, compared to placebo (10.9% vs 13.8%; P<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of a major coronary event, compared to placebo (7.7% vs 10.8%; P<0.0001). The difference in the reduction of the risk of major coronary events with statin therapy between the PAD and non-PAD groups was not statistically significant (P=0.03). In the overall study sample, simvastatin resulted in a significant 25% reduction in the first occurrence of stroke, compared to placebo (4.3% vs 5.7%; P<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of stroke, compared to placebo (5.3% vs 7.2%; P<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of stroke, compared to placebo (3.8% vs 5%; P<0.0001). The difference in the reduction of the risk of stroke with statin therapy between the PAD and non-PAD groups was not statistically significant (P=0.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the overall study sample, simvastatin resulted in a significant 24% reduction in the first occurrence of revascularization, compared to placebo (9.1% vs 11.7%; P<0.0001). Among patients with baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of revascularization, compared to placebo (13.8% vs 17.9%; P<0.0001). Among patients without baseline PAD, simvastatin resulted in a significant reduction in the first occurrence of revascularization, compared to placebo (6.9% vs 8.7%; P<0.0001). The difference in the reduction of the risk of revascularization with statin therapy between the PAD and non-PAD groups was not statistically significant (P=0.07). In the overall study sample, simvastatin resulted in a significant 16% reduction in the risk of first occurrence of a peripheral vascular event, compared to placebo (4.7% vs 5.5%; P=0.006). This risk reduction was independent of baseline LDL-C, age, diabetes, or coronary disease.
Ginsberg et al.[183] (2010) ACCORD Lipid Trial Simvastatin (dose titrated based on guidelines) and fenofibrate 160 mg daily vs simvastatin (dose titrated based on	RCT, OL, MC Patients 40-79 years of age with type 2 diabetes, A1C ≥7.5%, LDL-C 60 to 180 mg/dl, HDL-C <55 mg/dl (for women and blacks) or <50 mg/dl (all other groups), and TG <750 mg/dl (not receiving lipid therapy) or <400 mg/dl (receiving lipid therapy)	N=5,518 4.7 to 5 years	Primary: First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes Secondary: Primary outcome and revascularization or hospitalization for congestive	Primary: The annual rate of the primary outcome (first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR, 0.92; 95% CI, 0.79 to 1.08; P=0.32). Secondary: The hazard ratios for the secondary outcomes and the individual components of the primary outcome ranged from 0.82 to 1.17 (P≥0.10 for all comparisons). The annual rate of death from all causes was 1.5% in the fenofibrate group and 1.6% in the placebo group (HR, 0.91; 95% CI, 0.75 to 1.10; P=0.33). At the end of the study, the mean LDL cholesterol levels were 81.1 mg/dl in the fenofibrate group and 80.0 mg/dl in the placebo group. The mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
guidelines) and placebo			heart failure, combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina, nonfatal myocardial infarction, fatal or nonfatal stroke, nonfatal stroke, and death from any cause causes	HDL cholesterol levels were 41.2 mg/dl in the fenofibrate group and 40.5 mg/dl in the placebo group. Median plasma triglyceride levels were 147.0 mg/dl in the fenofibrate group and 170.0 mg/dl in the placebo group.
Baigent et al.[86] (2005) Statins (pravastatin 40 mg daily, fluvastatin 40-80 mg daily, simvastatin 20-40 mg daily, atorvastatin 10 mg daily, lovastatin 20-80 mg daily) vs placebo	MA Studies were included if the main effect of ≥1 trial interventions was lipid lowering, there was no confounder, and if ≥1,000 participants participated for at least 2 years.	N=90,056 (14 trials) ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death) in prespecified subgroups, effect on stroke, cancer, and vascular procedures, vascular events	Primary: There was a 12% reduction in all-cause mortality per 1 mmol/L reduction in LDL cholesterol (RR, 0.88, 95% CI, 0.84 to 0.91; P<0.0001). Statin therapy was associated with a 19% reduction in CHD mortality compared with control (3.4% vs 4.4%; RR, 0.81, 95% CI, 0.76 to 0.85; P<0.0001). Statin therapy was associated with a nonsignificant 17% reduction in non-CHD mortality compared with control (1.2% vs 1.3%; RR, 0.93, 95 % CI, 0.83 to 1.03). Secondary: Statin therapy was associated with a 17% reduction in vascular mortality compared with control (4.7% vs 5.7%; RR, 0.83, 95% CI, 0.79 to 0.87; P<0.0001). Statin therapy was associated with a 21% reduction in major vascular events (RR, 0.79, 95% CI, 0.77 to 0.81; P<0.0001). Statin therapy was associated with a 26% reduction in nonfatal MI (RR, 0.74, 99% CI, 0.70 to 0.79; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Statin therapy was associated with a 23% reduction in any major coronary event (RR, 0.77, 95% CI, 0.74 to 0.80; P<0.0001). Statin therapy was associated with a 24% reduction in any coronary revascularization (RR, 0.76, 95% CI, 0.73 to 0.80; P<0.0001). Statin therapy was associated with a 21% reduction in any stroke (RR, 0.79, 95% CI, 0.77 to 0.81; P<0.0001). Statin therapy was not associated with a significant increase in the incidence of rhabdomyolysis compared to control (P=0.4).
Cholesterol Treatment Trialists' Collaborators[87] (2008) Statins (pravastatin 40 mg daily, fluvastatin 40-80 mg daily, simvastatin 20-40 mg daily, atorvastatin 10 mg daily, lovastatin 20-80 mg daily) vs placebo	MA Studies were included if the main effect of ≥1 trial interventions was lipid lowering, there was no confounder, and if ≥1,000 participants participated for at least 2 years.	N=90,056 (14 trials) ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality among diabetes and non-diabetes patients Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death), major vascular events among diabetic and non-diabetic patients	Primary: Among patients with diabetes, there was a 9% reduction in all-cause mortality per each additional mmol/L reduction in LDL cholesterol (RR, 0.91, 99% CI, 0.82 to 1.01; P=0.02). Patients without diabetes experienced a 13% reduction in all-cause mortality per each additional mmol/L reduction in LDL cholesterol (RR, 0.87, 99% CI, 0.82 to 0.92; P<0.0001). Secondary: Patients with diabetes experienced a 13% reduction in vascular mortality per mmol/L reduction in LDL cholesterol (RR, 0.87, 99% CI, 0.76 to 1.00; P=0.008) and no effect on nonvascular mortality (RR, 0.97, 99% CI, 0.82 to 1.16; P=0.7). Among patients with diabetes, there was a 21% reduction in major vascular events per mmol/L reduction in LDL cholesterol (RR, 0.79, 99% CI, 0.72 to 0.86; P<0.0001). Patients without diabetes experienced a 21% reduction in major vascular events per mmol/L reduction in LDL cholesterol (RR, 0.79, 99% CI, 0.76 to 0.82; P<0.0001). Patients with diabetes experienced a 22% reduction in MI or coronary death (RR, 0.78, 99%CI, 0.69 to 0.87; P<0.0001), 25% reduction in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				coronary revascularization (RR, 0.75, 99% CI, 0.64 to 0.88; P<0.0001), and 21% reduction in stroke (RR, 0.79, 99% CI, 0.67 to 0.93; P=0.0002). After 5 years of treating 1,000 diabetic patients with statin therapy, 42 patients may be prevented from having a major vascular event (95% CI, 30 to 55). The benefit was greater among patients with diabetes and known vascular disease at baseline.
Secondary Prevention of Coronary Heart Disease Events				
Pitt et al.[88] (1999) AVERT Atorvastatin 80 mg daily vs percutaneous coronary transluminal angioplasty	MC, OL, R Patients, mean age 58.5 years, with stable CAD, LDL-C ≥115 mg/dL and TG ≤500 mg/dL, stenosis ≥50% in at least one coronary artery and had been recommended for treatment with percutaneous revascu-larization, asympto-matic or with Canadian Cardiovascular Society (CCS) class I or II angina, able to complete at least four minutes of a treadmill test or a bicycle exercise test without marked ECG changes indicative of ischemia	N=341 18 months	Primary: Number of ischemic events and/or need for revascularization, angina symptoms, adverse events	Primary: Compared to revascularization procedure, atorvastatin 80 mg daily was associated with a lower incidence of ischemic events (21% vs 13%; P=0.048). Compared to revascularization procedure, atorvastatin 80 mg daily resulted in a significantly longer time to the first ischemic event (P=0.03). Compared to revascularization procedure, atorvastatin 80 mg/day resulted in a significantly smaller improvement in the CCS classification of angina symptoms (54% vs 41%; P=0.009). The adverse events observed in the study were similar in the two treatment groups.
Knopp et al.[89] (2006) ASPEN	DB, MC, PG, RCT Adult patients between 40 and 75	N=2,410 4 years	Primary: Time to occurrence of the composite clinical end point	Primary: There was no statistically significant difference between atorvastatin and placebo groups in the time to first primary event (HR, 90; 95% CI, 0.73 to 1.12; P=0.034).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atorvastatin 10 mg once daily vs placebo once daily	years of age with type 2 diabetes, defined by the World Health Organization, for at least 3 years prior to screening, LDL cholesterol ≤140 mg/dL (if they had a history of an MI, or an interventional procedure >3 months before screening) or LDL cholesterol ≤160 mg/dL, triglyceride level ≤600 mg/dL		including cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG surgery, resuscitated cardiac arrest, worsening or unstable angina requiring hospitalization Secondary: Time to occurrence of cardiovascular death, non-cardiovascular death, transient ischemic attack, worsening or unstable angina not requiring hospitalization, worsening or unstable angina requiring hospitalization, surgery for newly diagnosed PAD, and acute ischemic heart failure requiring hospitalization, cholesterol level reduction, side effects	Less patients in the atorvastatin group experienced primary end points (13.7%) compared to the placebo group (15%) during the study period (P=0.034). Secondary: Atorvastatin group experienced a statistically significant decrease from baseline in the mean LDL-C (~29%) compared to the placebo group (1.6%; P<0.0001). Among patients without a prior history of an MI or interventional procedure, 10.4% of atorvastatin- and 10.8% of placebo-treated patients experienced a primary end point (HR, 97; 95% CI, 0.74 to 1.18). Among patients with a prior history of an MI or interventional procedure, 26.2% of atorvastatin- and 30.8% of placebo-treated patients experienced a primary end point (HR, 82; 95% CI, 0.59 to 1.15). Relative risk reductions in fatal and nonfatal MI were 27% overall (P=0.10), 19% for patients treated for primary protection (P=0.41), and 36% for patients treated for secondary protection (P=0.11). Adverse events were similar in both treatment groups for the total, primary, and secondary prevention groups. Serious adverse events occurred in 37.7% of patients in the atorvastatin groups and 35.4% of patients receiving placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Schwartz et al.[90] (2005) MIRACL Atorvastatin 80 mg daily within 96 hours of hospital admission with an acute coronary syndrome (ACS) vs placebo daily within 96 hours of hospital admission with an ACS	DB, MC, RCT Patients >18 years of age with unstable angina or non-Q-wave AMI, with chest pain or discomfort of at least 15 minutes duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and representing a change from their usual anginal pattern	N=3,086 16 weeks	Primary: A composite end point of death, nonfatal AMI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospital-ization but without new objective evidence of ischemia, coronary revascularization, time to occurrence of any of the above, and percent change in lipid levels from baseline, safety	Primary: Compared to placebo, atorvastatin 80 mg daily resulted in a 16% reduction in the risk of a composite end point of death, nonfatal AMI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia requiring hospitalization (17.4% vs 14.8%; P=0.048). Secondary: Compared to placebo, atorvastatin 80 mg daily resulted in a 26% reduction in the risk of a recurrent ischemia requiring hospitalization (RR, 0.74; 95% CI, 0.57 to 0.95; P=0.02). Compared to placebo, atorvastatin 80 mg daily resulted in a 50% reduction in the risk of a fatal and nonfatal stroke (RR, 0.50; 95% CI, 0.26 to 0.99; P=0.045). There were no significant differences between groups in the incidence of coronary revascularization procedures, worsening heart failure, worsening angina, occurrence of at least 1 secondary end point, or occurrence of at least 1 primary or secondary end point. Liver transaminase elevation was more common in the atorvastatin group than in the placebo group (2.5% vs 0.6%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Olsson et al.[91] (2007) MIRACL Atorvastatin 80 mg daily within 96 hours of hospital admission with an ACS vs placebo daily within 96 hours of hospital admission with an ACS	DB, MC, RCT Post hoc analysis of MIRACL study evaluating atorvastatin therapy in patients ≥65 years of age; patients >18 years of age with unstable angina or non-Q-wave AMI, with chest pain or discomfort of at least 15 minutes duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and representing a change from their usual anginal pattern	N=3,086 16 weeks	Primary: A composite end point of death, nonfatal AMI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization among patients ≥65 and <65 years of age Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, new or worsening heart failure requiring hospital-ization, worsening angina requiring hospitalization but without new objective evidence of ischemia, coronary revascu-larization, time to occurrence of any of the above, and percent change in	Primary: Compared to placebo, atorvastatin treatment led to a 14% reduction in the relative risk of the primary end point in patients ≥65 years of age (HR, 0.86; 95% CI, 0.70 to 1.07; ARR, 2.9%; P=0.18). Compared to placebo, atorvastatin treatment led to a 22% reduction in the relative risk of the primary end point in patients <65 years of age (HR, 0.78; 95% CI, 0.56 to 1.06; ARR, 2.5%; P=0.11). Secondary: There was no statistically significant difference in any of the secondary end points between the ≥65 and the <65 age groups (P>0.05). The frequency of adverse events was similar in all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			lipid levels from baseline among patients ≥65 and <65 years of age	
Athyros et al.[92] (2002) GREACE Atorvastatin 10 mg daily titrated up to 80 mg daily vs usual medical care, consisting of lifestyle modification, pharmacotherapy, including lipid-lowering agents	RCT Adult patients with established CHD not at LDL-C goal (<100 mg/dL), according to the NCEP criteria	N=1,600 3 years	Primary: Death, nonfatal MI, unstable angina, congestive heart failure, revascularization (coronary morbidity), and stroke Secondary: Safety	Primary: Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 51% reduction in the risk for CHD recurrent events or death (24.5% vs 12%; P<0.0001). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 43% reduction in all-cause mortality (5% vs 2.9%; P=0.0021). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 47% reduction in the risk of stroke (2.1% vs 1.1%; P=0.034). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 47% reduction in the risk of coronary mortality (4.8% vs 2.5%; P=0.0017). Compared to the usual care, atorvastatin 10 mg titrated to 80 mg daily was associated with a 54% reduction in the risk of coronary morbidity (P<0.0001). Atorvastatin 10 mg titrated to 80 mg daily was associated with a reduction in TC by 36%, LDL-C by 46%, TG by 31%, non–HDL-C by 44%, and an increase in HDL-C by 7%. Compared to the usual care, a greater proportion of patients randomized to atorvastatin therapy achieved the NCEP LDL-C treatment goals (3% vs 95%, respectively). Compared to the usual care, a greater proportion of patients randomized to atorvastatin therapy achieved the NCEP non–HDL-C treatment goals (14% vs 97%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Withdrawals due to adverse effects were similar in the atorvastatin and placebo groups (0.75% vs 0.4%).
Athyros et al.[93] (2007) GREACE Atorvastatin 10 mg daily titrated up to 80 mg daily vs usual medical care, consisting of lifestyle modification, pharmacotherapy, including lipid-lowering agents, for other risk factors (i.e., diabetes, hypertension)	SA Post hoc analysis of the GREACE study; adult patients with established CHD not at LDL-C goal (<100 mg/dL), according to the NCEP criteria, stratified by the presence of metabolic syndrome	N=1,600 3 years	Primary: Vascular events, estimated GFR, serum uric acid level	Primary: Compared to the usual care, daily statin therapy was associated with a 43% reduction in LDL-C from baseline (P<0.0001). Among patients with metabolic syndrome, statin therapy was associated with a significant 57% reduction in the incidence of vascular events compared with usual therapy (12.1% vs 28%; RR, 0.43; 95% CI, 0.20 to 0.64; P<0.0001). Among patients without metabolic syndrome, statin therapy was associated with a significant 41% reduction in the incidence of vascular events compared with usual therapy (RR, 0.59; 95% CI, 0.41 to 0.79; P<0.0001). Statin therapy was associated with a significant increase in GFR and a reduction in serum uric acid level from baseline (P<0.05), regardless of metabolic syndrome status. Usual therapy was associated with a significant reduction in GFR and an increase in serum uric acid level from baseline (P<0.05), regardless of metabolic syndrome status. Compared to patients without metabolic syndrome, patients with metabolic syndrome experienced a greater increase in GFR with statin therapy (P=0.02).
LaRosa et al.[108] (2005) TNT Atorvastatin 10 mg daily vs	DB, MC, PG, RCT Patients between 35-75 years of age, with CHD (either previous MI, coronary revascu-larization, angina with objective evidence of coronary disease)	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) Secondary:	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 22% reduction in the incidence of primary end point (10.9% vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; P=0.0002). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of strokes (3.1% vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.96; P=0.021).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atorvastatin 80 mg daily			Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event, side effects	Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events (5% vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; P=0.007). Each 1 mg/dl reduction in LDL-C was associated with a 0.6% relative risk reduction in cerebrovascular events (P=0.002) and a 0.5% relative risk reduction in stroke (P=0.041). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of nonfatal MIs (6.2% vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; P=0.004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major coronary events (8.3% vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0019). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events (26.5% vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; P<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of hospitalization for heart failure (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). There was no statistically significant difference between groups in the incidence of death from CHD (3.3% vs 2.4%; HR, 0.74; 95% CI, 0.59 to 0.94; P=0.01). There was no statistically significant difference between groups in the incidence of resuscitation after cardiac arrest (0.5%; HR, 0.96; 95% CI, 0.56 to 1.67; P=0.89).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no statistically significant difference between groups in the incidence of peripheral artery disease (5.6% vs 5.5%; HR, 0.97; 95% CI, 0.83-1.15; P=0.76). There was no statistically significant difference between groups in the incidence of death from any cause (5.6% vs 5.7%; HR, 1.01; 95% CI, 0.85 to 1.19; P=0.92). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of treatment-related adverse events (5.8% vs 8.1%; P<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of ALT/AST elevations >3 times the ULN (0.2% vs 1.2%; P<0.001).
Waters et al.[109] (2006) TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT Subanalysis of TNT study evaluating effects of high-dose atorvastatin on cerebrovascular events; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of primary end point (10.9% vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; P=0.0002). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of strokes (3.1% vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.86; P=0.021). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events (5% vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; P=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% relative risk reduction in cerebrovascular events (P=0.002) and a 0.5% relative risk reduction in stroke (P=0.041). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of nonfatal MIs (6.2% vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			coronary event	Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major coronary events (8.3% vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0019). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events (26.5% vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; P<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events (33.5% vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). There was no statistically significant difference between groups in the incidence of transient ischemic attacks (P=0.099). There was no statistically significant difference between groups in the incidence of death from CHD (P=0.087). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of treatment-related adverse events (5.8% vs 8.1%; P<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significantly higher incidence of ALT/AST elevations >3 times the ULN (0.2% vs 1.2%; P<0.001).
Deedwania et al.[110] (2006) TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of the TNT study evaluating effects of high-dose atorvastatin in patients with metabolic syndrome; patients between 35-75 years of age, with CHD (either previous	N=5,584 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with metabolic syndrome	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 29% reduction in the incidence of primary end point among patient with metabolic syndrome (13% vs 9.5%; HR, 0.71; 95% CI, 0.61 to 0.84; P<0.0001). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of cerebrovascular events among patients with metabolic syndrome (HR, 0.74; 95% CI, 0.59 to 0.93; P=0.011).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	MI, coronary revascularization, angina with objective evidence of coronary disease) and metabolic syndrome		Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients with metabolic syndrome	Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of major coronary events among patients with metabolic syndrome (HR, 0.72; 95% CI, 0.60 to 0.86; P=0.0004). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any coronary events among patients with metabolic syndrome (HR, 0.75; 95% CI, 0.67 to 0.83; P<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of any cardiovascular events among patients with metabolic syndrome (HR, 0.78; 95% CI, 0.71 to 0.85; P<0.0001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the incidence of hospitalization for congestive heart failure among patients with metabolic syndrome (HR, 0.73; 95% CI, 0.55 to 0.96; P=0.027). There was no statistically significant difference between groups in the incidence of all-cause mortality among patients with metabolic syndrome.
Shepherd et al.[111] (2006) TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of high-dose atorvastatin in patients with diabetes; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary	N=1,501 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with diabetes Secondary: Any occurrence of a major coronary event,	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 25% reduction in the incidence of primary end point among patients with diabetes (17.9% vs 13.8%; HR, 0.75; 95% CI, 0.58 to 0.97; P=0.026). Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant reduction in the time to any cardiovascular events among patients with diabetes (HR, 0.85; 95% CI, 0.73 to 1.00; P=0.044). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 31% reduction in the incidence of time to the first cerebrovascular event among patients with diabetes (HR, 0.69; 95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	disease) and diabetes, with LDL-C<130 mg/dL		cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients with diabetes	CI, 0.48 to 0.98; P=0.037). There was no statistically significant difference between groups in the incidence of cerebrovascular events among patients with diabetes (P=0.437). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of nonfatal MI among patients with diabetes (HR, 0.79; 95% CI, 0.55 to 1.14; P=0.202). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of fatal/nonfatal stroke among patients with diabetes (HR, 0.67; 95% CI, 0.43 to 1.04; P=0.075). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of death from CHD among patients with diabetes (HR, 0.74; 95% CI, 0.47 to 1.18; P=0.203). There was no statistically significant difference between groups in the incidence of major coronary events among patients with diabetes (P=0.922). There was no statistically significant difference between groups in the incidence of any coronary events among patients with diabetes (P=0.192). There was no statistically significant difference between groups in the incidence of any cardiovascular events among patients with diabetes (P=0.458). There was no statistically significant difference between groups in the incidence of major cardiovascular events among patients with diabetes (P=0.689). There was no statistically significant difference between groups in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				incidence of hospitalization with heart failure among patients with diabetes (P=0.277). There was no statistically significant difference between groups in the incidence of all-cause mortality among patients with diabetes (P=0.521). There was no statistically significant difference between groups in the incidence of PAD among patients with diabetes (P=0.789). There was no statistically significant difference between groups in the incidence of treatment-related adverse effects or persistent elevations in liver enzymes.
Wenger et al.[112] (2007) TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of the TNT study evaluating effects of high-dose atorvastatin in patients ≥65 years of age; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL	N=3,809 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients ≥65 years of age Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event	Primary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group experienced a significant 19% reduction in the incidence of primary end point among patients ≥65 years of age (12.6% vs 10.3%; HR, 0.81; 95% CI, 0.67 to 0.98; P=0.032). Consequently, in treating 35 patients with atorvastatin 80 mg versus atorvastatin 10 mg, one cardiovascular event could be prevented over a 5-year period. Secondary: Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of cerebrovascular events among patients ≥65 years of age (P=0.010). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of nonfatal MI among patients ≥65 years of age (HR, 0.79; 95% CI, 0.60-1.03; P=0.084). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of fatal/nonfatal stroke among patients ≥65 years of age (HR, 0.79; 95% CI, 0.57-1.09; P=0.158). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of death from CHD among patients ≥65 years of age (HR, 0.91; 95% CI, 0.63 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			among patients ≥65 years of age	1.29; P=0.59). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of resuscitated cardiac arrests among patients ≥65 years of age (HR, 1.19; 95% CI, 0.49 to 2.87; P=0.70). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of any cardiovascular events among patients ≥65 years of age (P<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of any coronary events among patients ≥65 years of age (P<0.001). Compared to atorvastatin 10 mg group, atorvastatin 80 mg group was associated with a significant reduction in incidence of hospitalization for heart failure among patients ≥65 years of age (P=0.008). There was no statistically significant difference between groups in the incidence of major coronary events among patients ≥65 years of age (P=0.128). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was not associated with a significant reduction in the incidence of death from cardiovascular causes among patients ≥65 years of age (HR, 0.91; 95% CI, 0.67 to 1.24; P=0.55). Compared to the atorvastatin 10 mg group, more patients in the atorvastatin 80 mg group died from non-cardiovascular causes among patients ≥65 years of age (HR, 1.26; 95% CI, 0.93 to 1.70; P=0.129). More patients ≥65 years of age randomized to the atorvastatin 80 mg group experienced treatment-related adverse events compared to the atorvastatin 10 mg group.
Khush et al.[113] (2007)	DB, MC, PG, RCT, SA	N=10,001	Primary: Hospitalization for	Primary: Prior history of heart failure is a significant risk factor for hospitalization

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	Post hoc analysis of TNT study evaluating effects of high-dose atorvastatin on hospitalization for heart failure; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL	5 years	heart failure among patients with and without a history of heart failure	from heart failure. While 14.1% of patients with heart failure at baseline were hospitalized for heart failure, only 1.9% of patients who did not have heart failure at baseline were hospitalized for heart failure during the study period (P<0.001). Compared to the atorvastatin 10 mg group, the atorvastatin 80 mg group was associated with a significant reduction in the incidence of hospitalization from heart failure among patients with heart failure at baseline (17.3% vs 10.6%; HR, 0.59; 95% CI, 0.4 to 0.80; P=0.008). Mortality was significantly higher among patients with heart failure compared to patients without heart failure at baseline (15% vs 4.9%; P<0.001). Each reduction of 1 mg/dL in LDL-C was associated with a reduction in the risk of hospitalization for heart failure by 0.6% (P=0.007).
LaRosa et al.[114] (2007) TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of VLDL-C levels achieved with atorvastatin on cardiovascular end points and mortality; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL	N=9,769 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with LDL-C <64 mg/dL (Quintile 1), 64 to ≤77 mg/dL (Quintile 2), 77 to ≤90 mg/dL (Quintile 3), 90 to ≤106 mg/dL (Quintile 4), and ≥106 mg/dL (Quintile 5)	Primary: Patients in the lowest quintiles were associated with the most reduction in the primary end point (P<0.0001). Secondary: Patients in the lowest quintiles were associated with the most reduction in the risk of death from CHD (P<0.01). Patients in the lowest quintiles were associated with the most reduction in the risk of nonfatal MIs (P<0.0001). Patients in the lowest quintiles were associated with the most reduction in the risk of stroke (P<0.05). There were no significant differences in the incidence of all-cause mortality across quintiles (P=0.104). There were no significant differences in the incidence of cardiovascular mortality across quintiles (P=0.060).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, peripheral artery disease, all-cause mortality, any cardiovascular event, and any coronary event among patients classified as Quintile 1, 2, 3, 4, or 5 (from above)	There were no significant differences in the incidence of all-cause mortality across quintiles (P=0.653). There were no significant differences in the incidence of treatment-related adverse effects across quintiles.
Barter et al.[115] (2007) TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Post hoc analysis of TNT study evaluating effects of HDL-C levels achieved with atorvastatin on cardiovascular end points; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130	N=9,770 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with HDL-C <38 mg/dL (Quintile 1), 38 to 42 mg/dL (Quintile 2), 43 to 47 mg/dL (Quintile 3), 48 to 54 mg/dL (Quintile 4), and ≥55 mg/dL (Quintile 5)	Primary: Patients in the highest HDL-C quintiles were associated with the greatest reduction in the primary end point (P=0.04). Compared to patients in Quintile 1, patients classified as Quintile 5 had a 25% reduction in risk of a major cardiovascular event (HR, 0.75; 95% CI, 0.60 to 0.95). An increase in 1 mg/dL in the HDL-C reduces the risk of major cardiovascular events by 1.1% at 3 months (P=0.003). Patients with the lowest ratio of LDL-C to HDL-C were at a lower risk for major cardiovascular events (P=0.006). Patients with the lowest ratio of TC to HDL-C were at a lower risk for major cardiovascular events. Among patients whose LDL-C was <70 mg/dL, those in the highest HDL-C quintile were at the lowest risk for a major cardiovascular event

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	mg/dL			(P=0.03).
Shepherd et al.[116] (2007) TNT Atorvastatin 10 mg daily vs atorvastatin 80 mg daily	DB, MC, PG, RCT, SA Subanalysis of TNT study evaluating nephro-protective effects of atorvastatin; patients between 35-75 years of age, with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) and diabetes, with LDL-C<130 mg/dL	N=9,770) 5 years	Primary: GFR	Primary: Patients randomized to atorvastatin 80 mg daily experienced a significant increase in GFR from baseline over a 5-year study period compared with the atorvastatin 10 mg daily group (P<0.0001).
Pedersen et al.[117] (2005) IDEAL Atorvastatin 80 mg daily vs simvastatin 20 mg daily	MC, OL, PG, RCT Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: Occurrence of a major coronary event (coronary death, confirmed nonfatal AMI, or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event and stroke), any CHD event (any primary event, any coronary revascularization	Primary: Atorvastatin therapy was associated with a nonsignificant reduction in the risk of a major coronary events compared with simvastatin therapy (9.3% vs 10.4%; HR, 0.89; P=0.07). Secondary: Atorvastatin therapy was associated with a significant reduction in the risk of a nonfatal MI compared with simvastatin therapy (6% vs 7.2%; HR, 83; P=0.02). Atorvastatin therapy was associated with a significant reduction in the risk of major cardiovascular events compared with simvastatin therapy (12% vs 13.7%; HR, 87; P=0.02). Atorvastatin therapy was associated with a significant reduction in the risk of any cardiovascular events compared with simvastatin therapy (26.5% vs 30.8%; HR, 84; P<0.001). Atorvastatin therapy was associated with a significant reduction in the risk

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			procedure, or hospitalization for unstable angina), any cardiovascular events	of any CHD event compared with simvastatin therapy (20.2% vs 23.8%; HR, 84; P<0.001). Atorvastatin therapy was associated with a significant reduction in the risk of peripheral vascular disease compared with simvastatin therapy (2.9% vs 3.8%; HR, 76; P=0.02). Atorvastatin therapy was associated with a nonsignificant reduction in the risk of death from non-cardiovascular cause compared with simvastatin therapy (3.2% vs 3.5%; HR, 92; P=0.47). Atorvastatin therapy was associated with a nonsignificant reduction in the risk fatal/nonfatal stroke compared with simvastatin therapy (3.4% vs 3.9%; HR, 87; P=0.20). Atorvastatin therapy was associated with a nonsignificant reduction in the risk hospitalization for nonfatal heart failure compared with simvastatin therapy (2.2% vs 2.8%; HR, 81; P=0.11). Atorvastatin therapy was associated with a nonsignificant reduction in the risk of all-cause mortality compared with simvastatin therapy (8.2% vs 8.4%; HR, 98; P=0.81). Atorvastatin therapy was associated with a higher rate of drug discontinuations due to adverse effects compared with simvastatin therapy (9.6% vs 4.2%; P<0.001). Atorvastatin therapy was associated with a higher rate of liver transaminase elevations compared with simvastatin therapy (P<0.001). There was no significant difference between treatment groups in the incidence of serious adverse events (P=0.42).
Cannon et al.[118] (2004) PROVE IT–TIMI 22 Atorvastatin 80 mg	DB, DD, MC, RCT Men and women ≥18 years of age (mean age 58.9 years), in stable condition after	N=4,162 Up to 3 years	Primary Rates of composite death from any cause, MI, documented unstable angina	Primary The rates of composite death from any cause, MI, unstable angina requiring hospitalization, revascularization, and stroke at two years were 26.3% in the pravastatin group and 22.4% in the atorvastatin group, representing a 16% reduction in the hazard ratio favoring atorvastatin (95% CI, 5% to 26%; P=0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs pravastatin 40 mg daily	a hospitalization for an ACS with either an AMI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to six months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL		requiring hospitalization, revascularization, and stroke Secondary Risk of death due to CHD, nonfatal MI, or revascularization and the risk of the individual components of the primary end points, discontinuation rates, tolerability and side effects	Secondary The risk of death due to CHD, nonfatal MI, or revascularization was reduced by 14% in the atorvastatin group (P=0.029) with a two-year event rate of 19.7% compared with 22.3% in the pravastatin group. The risk of death, MI, or urgent revascularization was reduced by 25% in the atorvastatin group (P<0.001). Among the individual components of the primary end point, atorvastatin-treated patients had significant reduction of 14% for revascularization (P=0.04) and a 29% reduction in the risk of recurrent unstable angina (P=0.02) compared to the pravastatin group. There were nonsignificant reductions in the rates of death or MI (18%, P=0.06) and the rates of stroke between the two groups. The discontinuation rates due to adverse events or for other reasons were 21.4% in the pravastatin group and 22.8% in the atorvastatin group at one year (P=0.30) and 33% and 30.4%, respectively at two years (P=0.11). Discontinuation rates due to myalgias or muscle aches or elevation in creatine kinase levels were 2.7% in the pravastatin group and 3.3% in the atorvastatin group (P=0.23). There were 1.1% of patients in the pravastatin group and 3.3% in the atorvastatin group who had elevations in ALT levels that were ≥3 times the ULN (P<0.001).
Ray et al.[119] (2005) PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	DB, RCT Subanalysis of PROVE IT-TIMI 22 study evaluating the timing of effects with statin therapy; patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours	N=4,162 Up to 3 years	Primary: A composite of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization, or stroke Secondary: A composite of death, MI, or unstable angina requiring	Primary: At 30 days, 3% of intensive regimen group experienced a primary end point compared with 4.2% in the standard treatment group (HR, 72; 95% CI, 0.52 to 0.99; P=0.046). From 6 months to the end of the study, 15.1% of intensive regimen group experienced a primary end point compared with 17.7% in the standard treatment group (HR, 82; 95% CI, 0.69 to 0.99; P=0.037). Secondary: Atorvastatin therapy was associated with a significant reduction in the risk of the triple composite end point compared with pravastatin therapy (15.7% vs 20%; HR, 76; 95% CI, 0.66 to 0.88; P=0.0002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hospitalization	At 30 days, patients randomized to the intensive statin regimen experienced a greater reduction in LDL-C and CRP level from baseline compared to the standard statin regimen group (P<0.001).
Ahmed et al.[120] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	RCT, SA Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin in patients with diabetes; patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours	N=4,162 Up to 3 years	Primary: A composite of death, MI, unstable angina requiring hospitalization, revascularization with PCI, or CABG surgery occurring within 30 days after randomization, or stroke within 2 years after study onset Secondary: A composite of death, MI, or unstable angina requiring hospitalization, LDL-C <70 mg/dL goal, hs-CRP <2 mg/L goal, MI, unstable angina requiring hospitalization	Primary: There was no statistically significant difference between the pravastatin and atorvastatin groups in terms of the primary end point among patients with diabetes (31.8% vs 28.4%; HR, 88; P=0.28). Secondary: Intensive atorvastatin therapy resulted in a significantly lower event rate for the secondary composite end point compared with the standard pravastatin regimen among patients with diabetes (21.1% vs 26.6%; HR, 0.75; P=0.03) and patients without diabetes (14% vs 18%; HR, 0.76; P=0.002). Consequently, treating 1,000 diabetic and nondiabetic patients with intensive statin regimen would prevent 55 and 40 events, respectively. Compared with nondiabetic patients, fewer patients with diabetes on the intensive statin regimen achieved the dual goal of LDL-C <70 mg/dL and hs-CRP <2 mg/L (37.6% vs 45.4%; P=0.004). Out of diabetic patients treated with intensive statin therapy, 62% failed to reach the dual goal of LDL-C <70 mg/dL and hs-CRP <2 mg/L. Diabetic patients who reached the dual LDL-C/CRP goal had significantly lower rates of the secondary end point compared to patients who failed to reach the goal (17.7% vs 24.7%; P=0.021). In the diabetic population, among the individual components of the primary and secondary composite end points, the only variable exhibiting a statistically significant reduction with intensive statin therapy compared with the standard regimen was unstable angina requiring hospitalization (3.1% vs 7.4%; P=0.003).
Scirica et al.[121] (2006)	DB, DD, RCT Subanalysis of	N=4,162 Up to 3	Primary: Hospitalization for heart failure	Primary: Patients randomized to the intensive statin group experienced a statistically significant reduction in the rate of hospitalization for heart

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	PROVE IT-TIMI 22 study evaluating effects of atorvastatin on hospitalization for heart failure; patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours, with TC <240 mg/dL	years	occurring at least 30 days after randomization	failure compared to the control group (1.6% vs 3.1%; HR, 0.55; 95% CI, 0.35 to 0.85; P=0.008). The benefit observed with the intensive statin therapy was independent on recurrent MI or prior history of heart failure. Higher B-type natriuretic peptide (BNP) was associated with an increased risk for heart failure (HR, 2.6; 95% CI, 1.2 to 5.5; P=0.016). Among patients with a high BNP level (>80 pg/mL), intensive statin therapy was associated with a lower incidence of heart failure compared to patients randomized to the standard statin regimen (HR, 0.32; 95% CI, 0.13 to 0.8; P=0.014).
Ray et al.[122] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	RCT, SA Subanalysis of PROVE IT-TIMI 22 study evaluating effects of atorvastatin in patients ≥70 years of age. Patients, mean age 58.9 years, with an ACS within 10 days of randomization, stable for at least 24 hours	N=4,162 Up to 3 years	Primary: Cardiac mortality, MI, unstable angina requiring hospitalization, relationship between NCEP goal and a composite primary end point of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization, or stroke Secondary: A composite of death, MI, or unstable angina requiring hospitalization	Primary: At 30 days, a greater proportion of patients in both age groups randomized to atorvastatin therapy achieved the NCEP goals compared with pravastatin therapy (P<0.001). Among the elderly, the achievement of the NCEP LDL-C goal was associated with an 8% reduction in the risk of primary end point from baseline (P=0.008). The younger age group achieving the NCEP LDL-C goal was associated with a 2.3% reduction in the risk of primary end point from baseline (P=0.013). Younger patients were associated with a lower risk of the primary composite end point compared to the older age group (23% vs 30.4%; P<0.0001). Younger patients were associated with a lower risk of all-cause mortality (P<0.0001), MIs (P<0.0001), unstable angina requiring hospitalization (P=0.01), or strokes (P=0.004) compared to the older age group. Secondary: The composite triple end point occurred more frequently in the elderly compared to the younger age group (20.1% vs 11%; HR, 1.93; 95% CI, 1.59 to 2.33; P<0.0001).
Deedwania et al.[123] (2007)	DB, DD, MC, PG, RCT	N=893 12 months	Primary: Absolute change in the total duration	Primary: At 12 months, the total duration of ischemia was significantly reduced from baseline in both groups (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SAGE Atorvastatin 80 mg daily (intensive regimen) vs pravastatin 40 mg daily (standard regimen)	Ambulatory CAD patients, between 65 and 85 years of age, with ≥1 episode of myocardial ischemia that lasted ≥3 minutes during a 48-hour ambulatory ECG at screening, and baseline LDL-C level between 100 mg/dL and 250 mg/dL		of myocardial ischemia on 48-hour Holter monitor from baseline to month 12 Secondary: Absolute change in the total duration of myocardial ischemia on 48-hour Holter monitor from baseline to month 3, the percent change in the total duration of myocardial ischemia from baseline to months 3 and 12, the absolute and percent change in the number of ischemic episodes from baseline to months 3 and 12, the percent change in ischemic burden, the proportion of patients free of ischemia at months 3 and 12, the percent change in the levels of TC,	There was no statistically significant difference between the pravastatin and atorvastatin groups in terms of the primary end point (P=0.88). Secondary: There were no statistically significant differences between the pravastatin and atorvastatin groups in any of the secondary end points assessing degree of ischemia at month 3 or 12. Atorvastatin therapy was associated with a 77% reduction in all-cause mortality relative to pravastatin therapy over a 12-months period (HR, 0.33; 95% CI, 0.13 to 0.83; P=0.014). Compared with pravastatin, therapy with atorvastatin was associated with a significantly greater reductions in TC, LDL-C, TG, and apo B at months 3 and 12 (P<0.001). Compared with atorvastatin, therapy with pravastatin was associated with a significantly greater increase in the level of HDL cholesterol at months 3 (P<0.001) and 12 (P=0.009). Atorvastatin therapy was associated with a higher incidence of liver test abnormalities compared to pravastatin therapy (17.3% vs 13.9%; P<0.001). There were no statistically significant differences between the pravastatin and atorvastatin groups in treatment related adverse events (13.9% vs 17.3%; P=0.17).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			LDL-C, HDL, TG, and apo B	
Serruys et al.[94] (2002) LIPS Fluvastatin 40 mg twice daily vs placebo twice daily	DB, MC, PC, RCT Men and women aged 18 to 80 years with angina or silent ischemia following successful completion of their first PCI, with baseline TC levels between 135 and 270 mg/dL, with fasting TG <400 mg/dL	N=1,677 3-4 years	Primary: Development of major adverse cardiac events (MACE), defined as cardiac death, nonfatal MI or a re-intervention procedure of CABG or repeat PCI Secondary: MACE excluding re-intervention procedures (surgical or PCI) occurring in the first 6 months of follow-up for lesions treated at the index procedure, cardiac mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI, and treatment effects on measured lipid levels, discontinuation rates, tolerability, and safety	Primary: MACE-free survival time was significantly longer in the fluvastatin group (P=0.01) compared to placebo. Significantly less patients in the fluvastatin group had a MACE compared to patients in the placebo group (21.4% vs 26.7%; RR, 0.78; 95% CI, 0.64 to 0.95; P=0.01). During the follow-up period, 13 patients in the fluvastatin group (1.5%) compared to 24 patients in the placebo group (2.9%) died from cardiac causes, 30 patients in the fluvastatin group (3.6%) compared to 38 patients in the placebo group (4.6%) had a nonfatal MI and 167 patients in the fluvastatin group (19.8%) compared to193 patients in the placebo group (23.2%) underwent CABG or PCI. Secondary: The risk of MACE, excluding re-intervention procedures (surgical or PCI), occurring in the first 6 months of follow-up for lesions treated at the index procedure was 33% lower (RR, 0.67; 95% CI, 0.54 to 0.8; P<0.001) in the fluvastatin group than in the placebo group. There was no difference in the reduction of cardiac mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI between the two groups (P=0.07, P=0.07 and P=0.08, respectively). At week 6, fluvastatin significantly reduced LDL-C by 27% (95% CI, 25% to 29%) compared with an 11% reduction seen in the placebo group (95% CI, 9% to 13%; P<0.001). Triglyceride reductions were greater in the fluvastatin group compared to placebo (22% vs 14%). Levels of HDL increased by a median of 22% in both groups. Discontinuation rates due to adverse events were 21.2% in the fluvastatin group and 24.0% in the placebo group. Death rates due to noncardiac

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				causes were 2.7% in the fluvastatin group and 3.0% in the placebo group. There were 3 reported cases of elevations in creatine kinase levels of ≥10 times the ULN in the placebo group. There were 10 patients in the fluvastatin group and 3 patients in the placebo group who had elevations of ≥3 times the ULN level in AST or ALT on 2 consecutive occasions. Cancers were reported in 46 patients in the fluvastatin group and 49 in the placebo group.
Liem et al.[95] (2002) FLORIDA Fluvastatin 80 mg daily vs placebo daily	DB, PC, PG, RCT Patients, mean age 61 years, with an AMI and TC of <6.5 mmol/L, new or markedly increased chest pain lasting >30 minutes, or a new pathological Q wave of ≥0.04 seconds duration, or ≥25% of the corresponding R wave amplitude, both in at least two contiguous leads	N=540 1 year	Primary Presence of either ischemia on ambulatory ECG monitoring at 12 months or the occurrence of a major clinical event during the study Secondary: 6-week and 12-month occurrence of ischemia on the ambulatory ECG, the 6-week and 12-month change in ischemic burden, the 12-month change in lipid profile, safety and tolerability	Primary: At 12 months, fluvastatin treatment did not significantly affect ischemia on ambulatory ECG (P=0.67), nor the occurrence of any major clinical event (P=0.24) when compared to placebo. Secondary: In patients with ischemia at baseline, 29% in the fluvastatin group and 38% in the placebo group were ischemic on the ambulatory ECG at 6 weeks and 27% in the fluvastatin group and 21% in the placebo group were again positive for ischemia at 12 months. The 6-week and 12-month ischemic burden was lowered by 6.1% and 7.7%, respectively in the fluvastatin group and by 10.5% and 13%, respectively in the placebo group (P=0.81 and P=0.43, respectively between treatment groups) After 12 months, treatment with fluvastatin lowered LDL-C by 21% compared to a 9% increase in the placebo group (P<0.001). There were 62 patients in the fluvastatin group and 68 patients in the placebo group who had at least one major clinical event (P=0.764). All-cause mortality was 2.6% in the fluvastatin group vs 4% in the placebo group.
Sacks et al.[96] (1996) CARE Pravastatin 40 mg	DB, MC, RCT Post MI patients, mean age 59 years, (including men and postmenopausal	N=4,159 5 years	Primary: Death from CHD (including fatal MI, either definite or probable, sudden death,	Primary: When compared with the placebo group, a 24% lower incidence of the primary end point was observed in the pravastatin group (13.2% vs 10.2%; 95% CI, 9% to 36%; P=0.003). Pravastatin therapy was associated with a 23% risk reduction in nonfatal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily vs placebo once daily	women), with plasma TC levels <240 mg/dL, LDL-C between 115-174 mg/dL, triglyceride <350 mg/dL, glucose levels ≤220 mg/dL, left ventricular ejection fractions ≥25 percent, and no symptomatic congestive heart failure		death during a coronary intervention and death from other coronary causes) or a symptomatic nonfatal MI confirmed by serum creatine kinase	MIs compared with placebo (P=0.02). The pravastatin group experienced a nonsignificant 37% reduction in the rate of fatal MIs (95% CI, –5 to 62; P=0.07) and a 25% reduction in the rate of total MIs (95% CI, 8 to 39; P=0.06) compared with placebo.
The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group[97] (1998) Pravastatin 40 mg once daily vs placebo once daily	DB, MC, PC Men and women 31 to 75 years of age, who were post MI or had a hospital discharge diagnosis of unstable angina between 3 and 36 months before study entry	N=9,014 6.1 years	Primary: Death from CHD Secondary: Incidence of MI, stroke, rate of CABG surgery	Primary: The incidence of the primary study end point of death from CHD was 6.4% in the pravastatin group, as compared with 8.3% in the placebo group (relative reduction in risk, 24%; 95% CI, 12% to 35%; P<0.001). Secondary: Pravastatin therapy was associated with a significant 29% reduction in the incidence of MI compared with placebo (7.4% vs 10.3%; P<0.001). Pravastatin therapy was associated with a significant 19% reduction in the incidence of stroke compared with placebo (3.7% vs 4.5%; P=0.048). Pravastatin therapy was associated with a significant 22% reduction in the risk of CABG surgery compared with placebo (9.2% vs 11.6%; P<0.001). Pravastatin therapy was associated with a significant 19% reduction in the risk of coronary angioplasty compared with placebo (4.7% vs 5.6%; P=0.024). Pravastatin therapy was associated with a significant 12% reduction in the risk of unstable angina compared with placebo (22.3% vs 24.6%; P=0.005).
Shepherd et al.[98] (2002)	DB, MC, PC, RCT	N=5,804	Primary: Combined end	Primary: Pravastatin therapy was associated with a significant 15% reduction in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PROSPER Pravastatin 40 mg once daily vs placebo once daily	Men and women aged 70-82 years with pre-existing vascular disease (coronary, cerebral, or peripheral) or at an increased risk of such disease due to risk factors (smoking, hypertension, or diabetes), with plasma TC 4.0-9.0 mmol/L, TG <6.0 mmol/L	Mean 3.2 years	point of definite or suspect death from CHD, nonfatal MI, and fatal or nonfatal stroke Secondary: Examination of coronary and cerebrovascular components separately, assessment of cognitive function, adverse events, cancer	risk of the primary end point compared to placebo (14.1% vs 16.2%; HR, 0.85; 95% CI, 0.74 to 0.97; P=0.014). Secondary: When the primary end point was separated into coronary and cerebrovascular components, the authors noted a 19% reduction in coronary events with pravastatin therapy, but no apparent effect on cerebrovascular events. Pravastatin therapy was associated with a significant 19% reduction in the risk of CHD death or nonfatal MI compared to placebo (10.1% vs 12.2%; HR, 0.81; 95% CI, 0.69 to 0.94, P=0.006). When examining the rates of fatal or nonfatal stroke, there was no significant difference between pravastatin and placebo (HR, 1.03; 95% CI, 0.81 to 1.31, P=0.81). There was no significant difference in cognitive function between the pravastatin and the placebo groups (P>0.05). The rate of serious adverse events reported was similar between both pravastatin and placebo groups (56% vs 55%, respectively). There were no participants in either group with rhabdomyolysis or CK concentrations greater than 10 times the ULN. There were no significant differences in the rates of cancer development between groups (P>0.05).
Thompson et al.[99] (2004) PACT Pravastatin 20-40 mg daily vs	DB, MC, PC, RCT Patients aged 18-85 years with <24 hours onset of symptoms and diagnosis of AMI or unstable angina pectoris	N=3,408 4 weeks	Primary: Composite of death from any cause, AMI, or readmission to hospital with unstable angina pectoris during the first month following	Primary: Pravastatin 40 mg was associated with a nonsignificant 6.4% reduction in the risk of the primary end point compared with placebo (P=0.48). Secondary: There were no significant differences in the frequency of individual components of the primary end point in the 30 days after random assignment among patients assigned to pravastatin compared to placebo (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo daily			randomization Secondary: Incidence of individual causes of death, AMI other than the index event, readmission for angina in the first month, urgent or unscheduled revascularization procedure, other nonfatal cardiovascular events, adverse events	The frequency of adverse events did not differ between the study groups.
Sato et al.[181] (2008) OACIS-LIPID Pravastatin 10 mg once daily vs no pravastatin	RCT, OL, MC Patients with acute myocardial infarction (AMI) and mild to moderate hyperlipidemia (TC 200-250 mg/dl and TH ≤300 mg/dl)	N=353 9 months	Primary: Composite end point of death, nonfatal myocardial infarction (MI), unstable angina, revascularization and non-fatal stroke, and rehospitalization because of other cardiovascular diseases	Primary: The composite end point occurred in 17.9% of patients in the pravastatin group compared to 31.4% of patients in the non-pravastatin group (HR, 0.56; 95% CI, 0.36–0.87; P<0.006). There were no significant differences in the risk of death (P=0.643), nonfatal MI (P=0.622), unstable angina (P=0.985), or nonfatal stroke (P=0.252) between the pravastatin group and non-pravastatin group. There was a lower risk of revascularization in the pravastatin group compared to the non-pravastatin group (12.7% vs 20.6%, P=0.049).
Tavazzi et al.[182] (2008) GISSI-HF	RCT, DB, MC, PC Patients ≥18 years of age with	N=4,631 Median 3.9 years	Primary: Time to death, and time to death or admission to	Primary: At the end of the follow-up period, 29% of patients in the rosuvastatin group died from any cause compared to 28% of patients in the placebo group (HR, 1·00; 97% CI, 0.898-1.122; P=0.943).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosuvastatin 10 mg once daily vs placebo	symptomatic heart failure (NYHA class II–IV)		hospital for cardiovascular reasons Secondary: Cardiovascular mortality, cardiovascular mortality or admission for any reason, sudden cardiac death, admission for any reason, admission for cardiovascular reasons, admission for heart failure, myocardial infarction, and stroke	The composite of all-cause death or admission to hospital for cardiovascular reasons occurred in 57% of patients in the rosuvastatin group compared to 56% of patients in the placebo group (HR, 1.01; 99% CI, 0.908–1.112; P=0.903). Secondary: There was no difference in cardiovascular mortality (P=0.804), first hospital admission for any, cardiovascular, or heart failure cause (P=0.962, P=0.613, and P=0.987, respectively), or the combined outcome measure of cardiovascular death or admission to hospital for any cause (P=0.409) sudden cardiac death (P=0.221), myocardial infarction (P=0.459), and stroke (P=0.174) with rosuvastatin compared to placebo.
Scandinavian Simvastatin Survival Study (4S) Group[100] (1994) Simvastatin 10 mg daily titrated up to 40 mg daily vs placebo daily	DB, PC, RCT Men and women, 35 to 70 years of age, with CHD, a history of angina pectoris or previous MI, and TC 212-309 mg/dL and triglyceride level <221 mg/dL on a lipid-lowering diet	N=4,444 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal AMI, resuscitated cardiac arrest, and definite silent MI)	Primary: Simvastatin therapy was associated with a 30% reduction in all-cause mortality compared with placebo (8% vs 12%; RR, 0.70; 95% CI, 0.58 to 0.85; P=0.0003). Secondary: Overall, more patients in the placebo group experienced at least one secondary event compared to the simvastatin group (28% vs 19%, respectively). There were 189 (8.5%) coronary deaths in the placebo group compared with 111 (5.0%) coronary deaths in the simvastatin group (RR, 0.58; 95% CI, 0.46 to 0.73). Definite AMI occurred in 270 (12.1%) patients in the placebo group compared with 164 (7.4%) patients in the simvastatin group. Definite or probable AMI occurred in 418 (18.8%) patients in the placebo group compared with 279 (12.6%) patients in the simvastatin group. Silent MI occurred in 110 (4.9%) patients in the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared with 88 (4.0%) patients in the simvastatin group. Resuscitated cardiac arrest occurred in 1 patient who was in the simvastatin group. Additionally, a cerebrovascular event occurred in 95 (4.3%) patients in the placebo group compared with 61 (2.7%) patients in the simvastatin group.
Chonchol et al.[101] (2007) Scandinavian Simvastatin Survival Study (4S) Simvastatin 10 mg daily titrated up to 40 mg daily vs placebo daily	SA Men and women, 35 to 70 years of age, with CHD, a history of angina pectoris or previous MI, and TC 212-309 mg/dL and triglyceride level <221 mg/dL on a lipid-lowering diet, stratified by estimated GFR of ≥75 mL/min/1.73 m2 or <75 mL/min/1.73 m2	N=4,444 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal AMI, resuscitated cardiac arrest, and definite silent MI)	Primary: Simvastatin therapy was associated with a significant reduction in all-cause mortality among patients with chronic renal insufficiency (HR, 0.70; 95% CI, 0.55 to 0.91). Secondary: Simvastatin therapy was associated with a significant reduction in the incidence of major coronary events among patients with chronic renal insufficiency (HR, 0.68; 95% CI, 0.57 to 0.80). Simvastatin therapy was associated with a significant reduction in the incidence of CHD deaths or nonfatal MIs among patients with chronic renal insufficiency (HR, 0.66; 95% CI, 0.55 to 0.79). Simvastatin therapy was associated with a significant reduction in the incidence of coronary revascularization among patients with chronic renal insufficiency (HR, 0.63; 95% CI, 0.51 to 0.79). Simvastatin therapy was not associated with a significant reduction in the incidence of strokes among patients with chronic renal insufficiency (HR, 0.86; 95% CI, 0.54 to 1.36). There were no statistically significant differences in any of the outcome measures between patients with or without chronic renal insufficiency (P>0.44).
de Lemos et al.[102] (2004) A to Z trial Simvastatin 40 mg daily for 1 month, titrated up to 80 mg	DB, MC, PC Patients with either non–ST-elevation ACS or ST-elevation MI; median of 61 years of age	N=4,497 2 years	Primary: Composite of cardiovascular death, nonfatal MI, readmission for ACS (requiring new ECG changes or cardiac marker	Primary: Simvastatin 80 mg therapy was associated with a significant reduction in the risk of the primary end point compared to simvastatin 20 mg therapy (14.4% vs 16.7%; HR, 0.89; 95% CI, 0.76 to 1.04; P=0.14). Secondary: Simvastatin 80 mg therapy was associated with a significant reduction in the risk of cardiovascular death compared to simvastatin 20 mg therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs placebo daily for 4 months, then simvastatin 20 mg daily			elevation), and stroke Secondary: Individual components of the primary end point, revascularization due to documented ischemia, all-cause mortality, new-onset congestive heart failure (requiring admission or initiation of heart failure medications), and cardiovascular rehospitalization	(HR, 0.75; 95% CI, 0.57 to 1.00; P=0.05). There was no significant difference observed between treatment groups in the secondary end points of MI, readmission for ACS, revascularization due to documented ischemia, or stroke (P>0.05). Simvastatin 80 mg therapy was associated with a significant reduction in the risk of new onset congestive heart failure compared to simvastatin 20 mg therapy (3.7% vs 5.0%; HR, 0.72; 95% CI, 0.53 to 0.98; P=0.04).
Brown et al.[166] (2001) Simvastatin + niacin (S+N) vs antioxidant vitamins vs simvastatin + niacin + antioxidant vitamins vs	RCT, PRO, DB, PC Men younger than 63 years of age and women younger than 70 years of age with clinical coronary disease and with at least three stenoses of at least 30 percent of the luminal diameter or one stenosis of at least 50 percent. All had low levels of HDL cholesterol (35 mg/dL or lower in men and 40 mg/dL in	N=160 3 year	Primary: Time to the first of the following events: death from coronary causes, nonfatal myocardial infarctions, stroke, or revascularization for worsening ischemia. Secondary: Lipid, lipoprotein levels	Primary: The risk of the composite primary end point was 90% lower in the S+N group than in the placebo group (P=0.03). The mean percent stenosis increased by 1.8% after antioxidant therapy, and decreased by 0.4% (P<0.001) after S+N therapy. With S+N plus antioxidants, proximal stenosis increased by 0.7% (P=0.004). Secondary: Antioxidants did not affect lipid levels except for the level of HDL2 (considered to be the most protective component of HDL), which was lowered by 15% in the group that received only antioxidants (P=0.05 for the comparison with the placebo group). The base-line levels of LDL cholesterol and TG decreased by 42% and 36%, respectively, with S+N therapy alone and decreased similarly when antioxidants were added to the regimen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	women), LDL cholesterol levels of 145 mg/dL or lower, and TG levels below 400 mg/dL			The HDL level increased by 26% in those treated with S+N alone and by 18% with added antioxidants (P=0.05). With S+N therapy alone, the levels of HDL2 and lipoprotein (A-I) increased by 65% and 81% respectively. These responses were specifically blunted when antioxidants were added to the regimen (increases of 28 % [P=0.02 for the comparison with the S+N group] and 28% [P=0.01] respectively). The levels and composition of lipoprotein (A-I, A-II) were not altered by S+N therapy, antioxidants, or the combination of the two.
Briel et al.[103] (2006) Statins (pravastatin 10-40 mg, fluvastatin 80 mg, atorvastatin 20-80 mg, simvastatin 40-80 mg) vs placebo	MA Randomized, placebo-controlled trials in patients with ACS (MI or unstable angina), started on statin therapy within 14 days of ACS, and with a follow-up ≥30 days	N=13,024 (12 trials) ≥30 days	Primary: Composite end point of nonfatal MI, nonfatal stroke, and total death Secondary: Total death, total MI, total stroke, cardiovascular death, fatal/nonfatal MI, revascularization procedures (CABG surgery, angioplasty), and unstable angina (recurrent myocardial ischemia requiring emergency hospitalization)	Primary: At either Month 1 or Month 4 of follow-up, there was no statistically significant difference in the primary end point between patients randomized to early statin therapy or placebo (P=0.39 and P=0.30, respectively). Secondary: At either Month 1 or Month 4 of follow-up, there was no statistically significant difference in any of the secondary end points (except for unstable angina) between patients randomized to early statin therapy or placebo. At 4 months of therapy, patients in the early statin group experienced moderate reduction in the incidence of unstable angina compared to the placebo group (P=0.05).
Mood et al.[104] (2007)	MA Randomized	N=3,941 (6 trials)	Primary: Incidence of an MI	Primary: Compared to placebo, statin therapy was associated with a 43% reduction in the risk for MI (5.2% vs 3.0%; OR, 0.57; 95% CI, 0.42 to 0.78;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Statins (atorvastatin 20-40 mg daily, pravastatin 40 mg daily, fluvastatin 40 mg twice daily) vs placebo	controlled studies comparing statin therapy to placebo or usual care, initiated around the time of a PCI	Up to 45 months	Secondary: All-cause mortality, cardiovascular mortality, surgical or percutaneous revascularization, or stroke	P<0.0001). Secondary: Compared to placebo, statin therapy was associated with a 26% reduction in all-cause mortality (3% vs 2.3%; OR, 0.74; 95% CI, 0.50 to 1.1; P=0.14). Compared to placebo, statin therapy was associated with a 42% reduction in cardiovascular mortality (1.2% vs 0.71%; OR, 0.58; 95% CI, 0.30 to 1.11; P=0.10). Compared to placebo, statin therapy was associated with an 11% reduction in the incidence of repeat surgical or percutaneous revascularization (21.9% vs 19.6%; OR, 0.89; 95% CI, 0.78 to 1.02; P=0.098). The incidence of stroke was higher in the statin group compared to the placebo arm (0.4% vs 0.08%; OR, 3.00; 95% CI, 0.60 to 14.77; P=0.18).
Afilalo et al.[105] (2008) Statins (pravastatin 40 mg daily, fluvastatin 80 mg daily, simvastatin 20-40 mg daily) vs placebo	MA Randomized controlled trials with at least 6 months of follow-up evaluating ≥50 elderly patients with CHD randomized to a statin or placebo	N=19,569 (9 trials) ≥6 months	Primary: All-cause mortality, CHD mortality, stroke, revascularization, nonfatal MI	Primary: Statin therapy was associated with a lower rate of all-cause mortality compared with placebo (15.6% vs 18.7%; RR, 0.78; 95% CI, 0.65 to 0.89). Statin therapy was associated with a reduction in the risk of CHD mortality by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), nonfatal MI by 26% (RR, 0.74; 95% CI, 0.60 to 0.89), revascularization by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), and stroke by 25% (RR, 0.75; 95% CI, 0.56 to 0.94). The calculated number needed to treat with statin therapy to save 1 life was 28 (95% CI, 15 to 56).
Bushnell et al.[106] (2006) Statins vs	MA Patients with CHD or vascular disease	N=22,943 90 days	Primary: Incidence of stroke at 90 days, stroke severity, mortality from strokes, differences between sexes	Primary: Patients reporting the use of statin therapy had lower rates of stroke at 90 days of follow-up (HR, 0.72; 95% CI, 0.53-0.97). Statin use was not associated with a significant reduction in stroke mortality (P=0.8).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no statins				Women had an increased risk of experiencing a severe stroke compared with men (P=0.035). Statin use was not associated with a significant reduction in stroke severity among women (P=0.096).
O'Regan et al.[107] (2008) Statins (atorvastatin 10-80 mg, simvastatin 20-40 mg, fluvastatin 40-80 mg, pravastatin 10-40 mg, lovastatin 20-73 mg) vs placebo	MA Randomized trials evaluating the effect of statin therapy on all-cause mortality, all-stroke incidence, fatal strokes, hemorrhagic, or ischemic strokes	N=121,285 (42 trials) Up to 6 years	Primary All-cause mortality, all-stroke incidence Secondary Incidence of cardiovascular deaths, non-hemorrhagic cerebrovascular events, hemorrhagic strokes, fatal strokes	Primary Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of all-cause mortality (RR, 0.88; 95% CI, 0.83 to 0.93). Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of strokes (RR, 0.84; 95% CI, 0.79 to 0.91). Secondary: Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of cardiovascular death (RR, 0.81; 95% CI, 0.74 to 0.90). Compared to placebo, statin therapy was associated with a statistically significant reduction in the risk of non-hemorrhagic cerebrovascular events (RR, 0.81; 95% CI, 0.69 to 0.94). Compared to placebo, statin therapy was associated with a statistically nonsignificant reduction in the risk hemorrhagic strokes (RR, 0.94; 95% CI, 0.68 to 1.30). Compared to placebo, statin therapy was associated with a statistically nonsignificant reduction in the risk of fatal strokes (RR, 0.99; 95% CI, 0.80 to 1.21). A meta-regression analysis determined that every unit increase in LDL was associated with a 0.3% increased risk of mortality (RR, 1.003; 95% CI, 0.1.0005 to 1.006; P=0.02).
Sakamoto et al.[22] (2007)	I, MC, RCT Patients, mean age	N=486 416 days	Primary: A composite end point of ACS	Primary: Hydrophilic statin therapy was associated with a lower incidence of ACS events compared to the lipophilic statin therapy (3.6% vs 9.9%; P=0.053).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MUSASHI-AMI Lipophilic statins* (atorvastatin 9.3 mg, fluvastatin 26.8 mg, pitavastatin 2 mg, simvastatin 5 mg) within 96 hours of hospital admission with an AMI vs hydrophilic statin* (pravastatin 9.4 mg) within 96 hours of hospital admission with an AMI *Doses represent the mean daily doses evaluated in the study.	63.5 years, randomized to statin or no statin therapy within 96 hours of an AMI, with TC between 190 and 240 mg/dL		events, such as cardiovascular death, nonfatal MI, recurrent acute myocardial ischemia requiring emergency hospitalization Secondary: Occurrence of the individual components of the primary end point, nonfatal stroke, heart failure requiring emergent rehospitalization, new Q-wave appearance on the ECG	Secondary: Hydrophilic statin therapy was associated with a lower incidence of new Q-wave appearance on the ECG compared to the lipophilic statin therapy (75% vs 89%; P=0.0056). There was no statistically significant difference in any of the other secondary end points between the two groups (P=0.339).
Hulten et al.[124] (2006) Intensive statin therapy (pravastatin 40 mg daily, fluvastatin 80 mg daily, simvastatin 80 mg daily, atorvastatin 20 mg daily, atorvastatin 80 mg daily) vs	MA Randomized controlled trials in adults started on intensive statin therapy or control within 14 days of hospitalization for ACS	N=17,963 (13 trials) Up to 2 years	Primary: Composite end point of death, recurrent ischemia, and recurrent MI, death and cardiovascular events, cardiovascular death, ischemia, MI, LDL-C reduction, side effects	Primary: In patients with recent ACS, intensive statin therapy was associated with lower mortality and cardiovascular events over 24 months of follow-up (HR, 0.81; 95% CI, 0.77 to 0.87; P<0.001). In patients with recent ACS, intensive statin therapy was associated with a lower risk of overall cardiovascular events over 24 months of follow-up (HR, 0.84; 95% CI, 0.76 to 0.94). In patients with recent ACS, intensive statin therapy was associated with lower cardiovascular mortality over 24 months of follow-up (HR, 0.76; 95% CI, 0.66 to 0.87). In patients with recent ACS, intensive statin therapy was associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo or lower-dosed statin therapy				lower ischemia over 24 months of follow-up (HR, 0.68; 95% CI, 0.50 to 0.92). In patients with recent ACS, intensive statin therapy was not associated with a lower incidence of MIs over 24 months of follow-up (HR, 0.89; 95% CI, 0.60 to 1.33). Intensive statin therapy was associated with a greater reduction in LDL-C compared with controls (P<0.001). Adverse effects were similar with the intensive statin therapy and the controls.
Afilalo et al.[125] (2007) Moderate statin therapy (pravastatin ≤40 mg daily, lovastatin ≤40 mg daily, fluvastatin ≤40 mg daily, simvastatin ≤20 mg daily, atorvastatin ≤10 mg daily, rosuvastatin ≤5 mg daily) vs intensive statin therapy (simvastatin 80 mg daily, atorvastatin 80 mg daily, rosuvastatin 20-40 mg daily)	MA Randomized controlled trials with at least 6 months of follow-up evaluating patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=28,505 (6 trials) ≥6 months	Primary: All-cause mortality, CHD mortality, hospitalization for heart failure, major coronary event (cardiovascular death or ACS), stroke, adverse effects	Primary: In patients with recent ACS, intensive statin therapy was associated with lower all-cause mortality (OR, 0.75; 95% CI, 0.61 to 0.93). By treating 90 people with intensive statin therapy, one death could be prevented. All-cause mortality was not reduced by intensive statin therapy among patients with stable CHD (OR, 0.99; 95% CI, 0.89 to 1.11). In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.86; 95% CI, 0.73 to 1.01). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.82; 95% CI, 0.75 to 0.91). Treating 46 patients with intensive statin therapy may prevent one major coronary event. In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.63; 95% CI, 0.46 to 0.86). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.77; 95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CI, 0.64-0.92). Treating 112 patients with intensive statin therapy may prevent one hospitalization for heart failure. Intensive statin therapy was associated with a threefold increase in adverse hepatic (OR, 3.73; 95% CI, 2.11 to 6.58) and muscular events (OR, 1.96; 95% CI, 0.50 to 7.63). Consequently, 96 people would need to be treated, for one patient to experience an adverse hepatic event.
Cannon et al.[126] (2006) Intensive statin therapy (simvastatin 40-80 mg daily, atorvastatin 80 mg daily) vs moderate statin therapy (pravastatin 40 mg daily, simvastatin 20 mg daily, atorvastatin 10 mg daily)	MA Randomized controlled trials evaluating patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=27,548 (4 trials) Up to 5 years	Primary: Combined incidence of coronary death or nonfatal MI, the combined incidence of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina, or revascularization), incidence of stroke, incidence of cardiovascular, non-cardiovascular, and all-cause mortality	Primary: Intensive statin therapy was associated with an overall significant odds reduction of 16% for coronary death or MI compared to moderate statin therapy (9.4% vs 8.0%; OR, 0.84; 95% CI, 0.77 to 0.91; P<0.00001). Intensive statin therapy was associated with an overall significant odds reduction of 16% for coronary death or any cardiovascular event compared to moderate statin therapy (32.3% vs 28.8%; OR, 0.84; 95% CI, 0.80 to 0.89; P<0.0000001). Intensive statin therapy was associated with a reduction in cardiovascular mortality of 12% compared to moderate statin therapy (3.8% vs 3.3%; OR, 0.88; 95% CI, 0.78 to 0.1.00; P=0.054). Intensive statin therapy was not associated with lower non-cardiovascular mortality compared to the moderate statin therapy (P=0.73). Intensive statin therapy was not associated with statistically significant reduction in all-cause mortality compared to the moderate statin therapy (6.2% vs 5.9%; P=0.20). Intensive statin therapy was associated with an overall significant odds reduction of 18% for stroke compared to moderate statin therapy (2.8% vs 2.3%; OR, 0.82; 95% CI, 0.71 to 0.96; P=0.012). Intensive statin therapy was associated with an overall significant odds reduction of 16.5% for CHD death or MI compared to moderate statin therapy (OR, 0.835; 95% CI, 0.77 to 0.91; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Murphy et al.[127] (2007) A to Z PROVE-IT-TIMI 22 Intensive statin therapy (simvastatin 40-80 mg daily, atorvastatin 80 mg daily) vs moderate statin therapy (pravastatin 40 mg daily, simvastatin 20 mg daily)	MA Randomized controlled trials evaluating patients with recent ACS, clinically stable for 12-24 hours, randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=8,658 (2 trials) Up to 2 years	Primary: Incidence of cardiovascular, non-cardiovascular, and all-cause mortality	Primary: Intensive statin therapy was associated with a significant 23% reduction in the risk of all-cause mortality, compared to moderate statin therapy (3.6% vs 4.9%; HR, 0.77; 95% CI, 0.63 to 0.95; P=0.015). Intensive statin therapy was associated with a significant 24% reduction in the risk of cardiovascular mortality, compared to moderate statin therapy (2.6% vs 3.5%; HR, 0.76; 95% CI, 0.59 to 0.97; P=0.025). Intensive statin therapy was not associated with a significant reduction in the risk of non-cardiovascular mortality, compared to moderate statin therapy (1% vs 1.4%; HR, 0.82; 95% CI, 0.55 to 1.21; P=0.32).
Delaying the Progression of Atherosclerosis				
Yu et al.[28] (2007) Atorvastatin 80 mg once daily vs atorvastatin 10 mg once daily	DB, RCT Patients with CHD (confirmed by angiographic evidence of coronary stenosis, previous MI, PCI, or angina pectoris), hypercholesterolemia and an LDL-C >100 mg/dL	N=112 26 weeks	Primary: Improvement in IMT Secondary: Reduction in CRP level, and proinflammatory cytokines at week 26	Primary: While atorvastatin 10 mg therapy was not associated with a statistically significant improvement in either left or right carotid IMT, atorvastatin 80 mg therapy led to a significant improvement in left carotid IMT (P=0.02) as well as the right carotid IMT from baseline (P=0.01). Secondary: While atorvastatin 10 mg therapy was not associated with a statistically significant change in CRP, atorvastatin 80 mg therapy led to a significant reduction in CRP level from baseline (P=0.01). In terms of proinflammatory cytokines, atorvastatin 10 mg therapy was associated with a statistically significant reduction in interleukin-8 (P=0.01), interleukin-18 (P<0.001), and tumor necrosis factor (P<0.001). Atorvastatin 80 mg therapy led to a significant reduction in all the proinflammatory cytokines from baseline (P<0.05).
Schmermund et al.[29]	DB, MC, RCT	N=471	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Atorvastatin 10 mg once daily vs atorvastatin 80 mg once daily	Patients between the ages of 32 and 80 years without a history of MI, coronary revascularization, or hemodynamically relevant stenoses, with moderate calcified coronary atherosclerosis (coronary artery calcification [CAC] score ≥30), LDL-C between 130 and 250 mg/dL in the absence of statin therapy or between 100 and 130 mg/dL under statin therapy, TG <400 mg/dL, ≥2 cardiovascular risk factors	12 months	The percent change in total CAC volume score Secondary: Change in LDL-C	There was no significant difference in the primary end point between the two groups (P=0.6477). Secondary: Atorvastatin 80 mg therapy was associated with a 20% reduction in LDL-C compared to atorvastatin 10 mg therapy.
Nissen et al.[30] (2004) REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo	DB, MC, RCT Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis	N=654 18 months	Primary: Percentage change in atheroma volume from baseline Secondary: Nominal change in atheroma volume, nominal change in atheroma volume in the 10 contiguous cross-	Primary: Atorvastatin therapy was associated with a significant delay in atheroma volume progression compared to pravastatin therapy (P=0.02). Secondary: Atorvastatin therapy was associated with a significant nominal change in total atheroma volume compared to pravastatin therapy (P=0.02). Atorvastatin therapy was associated with a significant change in the percentage of atheroma volume compared to pravastatin therapy (P<0.001). Atorvastatin therapy was associated with a significant change in atheroma

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
once daily	>50% in a target segment >30 mm long		sections with the greatest and the least atheroma volume	volume in the most severely diseased 10 mm vessel subsegment compared to pravastatin therapy (P=0.01). Progression of coronary atherosclerosis from baseline occurred in the 2.7% of the pravastatin-treated patients (P=0.001) and none of the atorvastatin-treated patients (P=0.98). Atorvastatin 80 mg daily therapy was associated with a significant reduction in TC, LDL-C, TG, apo B, and CRP (P<0.001) compared with the pravastatin group.
Schoenhagen et al.[31] (2006) REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT Serial intravascular ultrasound observations from the REVERSAL study. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	N=654 18 months	Primary: Percentage change from baseline in external elastic membrane area lesion, lumen area lesion, plaque area lesion, remodeling ratio	Primary: Atorvastatin therapy was associated with a significant 6.6% increase in the external elastic membrane area lesion from baseline (P<0.0001). Atorvastatin therapy was associated with a significant 7.3% increase in the lumen area lesion from baseline (P=0.0002). Atorvastatin therapy was associated with a significant 7.9% increase in the plaque area lesion from baseline (P=0.0002). Atorvastatin therapy was associated with a significant 3.3% reduction in remodeling ratio from baseline (P=0.024). Pravastatin therapy was associated with a significant 9% increase in the external elastic membrane area lesion from baseline (P=0.0002). Pravastatin therapy was associated with a significant 9.5% increase in the lumen area lesion from baseline (P=0.0003). Pravastatin therapy was associated with a significant 9.9% increase in the plaque area lesion from baseline (P=0.0022). Pravastatin therapy was associated with a significant 2.7% reduction in remodeling ratio from baseline (P=0.0013). There was no statistically significant difference between the atorvastatin intensive therapy and the pravastatin groups in terms of increase in plaque

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				area from baseline (7.9% vs 9.9%, respectively; P=0.57). There was no statistically significant difference between the atorvastatin (intensive) therapy and the pravastatin (moderate) groups in terms of reduction in remodeling ratio from baseline (3.3% vs 2.7%, respectively; P=0.68).
Nicholls et al.[32] (2006) REVERSAL Atorvastatin 40 mg twice daily vs pravastatin 40 mg once daily in addition to placebo once daily	DB, MC, RCT, SA Subanalysis of REVERSAL study in obese patients. Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI>29.6 kg/m^2 or BMI<29.6 kg/m^2	N=654 18 months	Primary: Percentage change from baseline in lipid parameters, atheroma volume	Primary: Compared to the BMI<29.6 kg/m2 group, obese patients on atorvastatin therapy exhibited a significantly lower reduction in TC (40% vs 36%; P=0.007), LDL-C (55% vs 49%; P=0.008), and TG (35% vs 23%; P=0.04). Compared to the BMI<29.6 kg/m2 group, obese patients on atorvastatin therapy exhibited a significantly higher reduction in CRP (33% vs 40%; P=0.04). There was no significant difference in lipid parameters between the BMI groups among patients randomized to pravastatin therapy (P>0.05). Compared to the BMI<29.6 kg/m2 group, obese patients on atorvastatin therapy exhibited a significantly greater benefit on the total atheroma volume (P=0.01) and percent atheroma volume (P=0.0005). In contrast, pravastatin therapy was associated with a significant 6.5% increase in atheroma volume in the obese group (P=0.006).
Nissen et al.[33] (2005) REVERSAL Atorvastatin 40 mg twice daily vs	DB, MC, RCT Subanalysis of REVERSAL study evaluating the effect of statin therapy on LDL, CRP, and CAD. Patients 30 to 75 years of age with >1 angiographic luminal	N=654 18 months	Primary: Percent change in TC, TG, CRP, non–HDL-C, HDL-C, atheroma volume	Primary: Patients in both treatment groups experienced a significant reduction from baseline in the TC (63%; P<0.001), LDL-C (56%; P<0.001), TG (40%; P=0.002), CRP (22.4%; P<0.001) and non–HDL-C (33%; P<0.001). HDL-C was not significantly increased from baseline in either group (4.2%; P=0.11). Patients randomized to atorvastatin experienced a slower rate of disease progression (atheroma volume) compared to patients receiving pravastatin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pravastatin 40 mg once daily in addition to placebo once daily	narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C between 125 and 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI>29.6 kg/m2 or BMI<29.6 kg/m2			therapy (0.2% vs 1.6%). Patients whose LDL-C and CRP reductions were greater than the median experienced a significantly slower rate of disease progression compared with patients with lower LDL-C and CRP reductions (P=0.001).
Furberg et al.[23] (1994) ACAPS Lovastatin 20 to 40 mg once daily in addition to warfarin 1 mg once daily vs lovastatin 20 to 40 mg once daily in addition to warfarin placebo once daily vs lovastatin placebo once daily in addition to warfarin 1 mg once daily	DB, MC, PC, RCT Asymptomatic men and women 40 to 79 years old, with early carotid atherosclerosis as defined by B-mode ultrasonography and moderately elevated LDL cholesterol (LDL levels between the 60th and 90th percentiles)	N=919 3 years	Primary 3-year change in the mean maximum IMT in 12 walls of the carotid arteries (near and far walls of the common carotid, the bifurcation, and the internal carotid arteries on both sides of the neck) Secondary Change in single maximum IMT, incidence of major cardiovascular events and adverse events	Primary The progression rate of mean maximum IMT was less in the lovastatin and warfarin combination group than in the lovastatin group alone (*P*=0.04). The overall annualized progression rates of mean maximum IMT in the lovastatin group and placebo group were –0.009 and 0.006 mm/year, respectively (*P*=0.001). Secondary: The changes in single maximum IMT in the lovastatin group and placebo group were –0.036±0.022 mm/year and 0.000±0.011 mm/year, respectively (*P*=0.12). Fourteen of the 459 patients in the lovastatin-placebo groups had a major cardiovascular event (4 CHD deaths, 5 strokes and 5 nonfatal myocardial infarction) compared with 5 of the 460 patients in the lovastatin group (*P*=0.04). There was 1 death in patients treated with lovastatin and 8 deaths in patients receiving lovastatin-placebo therapy (*P*=0.02). All 6 cardiovascular deaths were in the lovastatin-placebo group, the remaining 3 deaths were cancer deaths. The lovastatin and lovastatin-placebo groups showed no difference in ALT elevations of ≥200% the ULN.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs lovastatin placebo once daily in addition to warfarin placebo once daily				
Byington et al.[24] (1995) PLAC-II Pravastatin 20 mg once daily in the evening, titrated up to 40 mg daily vs placebo	DB, PC, RCT Patients with a history of CHD and ≥1 extracranial carotid lesion with the maximum IMT ≥1.3 mm	N=151 3 years	Primary: Change in the mean of maximum IMT measurements in the common, internal, and bifurcation carotid artery segments Secondary: Effects on individual carotid artery segments and clinical events	Primary: Pravastatin treatment did not result in a statistically significant reduction in the progression of mean maximum IMT (P=0.44). Pravastatin treatment was associated with a 35% statistically significant reduction in IMT progression in the common carotid artery (P=0.03). There was no significant effect on bifurcation (P=0.49) or on the internal carotid artery (P=0.93) with pravastatin therapy. Secondary: Pravastatin treatment was associated with a 60% reduction in clinical coronary events (P=0.09). When compared to placebo, a significant 61% reduction in the incidence of any coronary events and all-cause mortality was seen in the pravastatin group (P=0.04).
Meaney et al.[186] (2009) VYCTOR Pravastatin 40 mg once daily (ezetimibe 10 mg could be added if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions)	RCT, OL Patients 40 to 72 years of age with a 10-year absolute risk for coronary death or myocardial infarction ≥20 according to the ATP III recommendations	N=90 1 year	Primary: Change in carotid intima-media thickness (IMT) Secondary: Changes in LDL-C and high sensitive C-reactive protein (hs-CRP)	Primary: After 1 year, IMT values were 0.93mm (-30%; P<0.01 vs baseline), 0.90 mm (-30%; P<0.01 vs baseline), and 0.92 mm (-25%; P<0.01 vs baseline) for pravastatin, simvastatin, and simvastatin/ezetimibe groups, respectively. There was no significant difference among the treatment groups. Secondary: At the end of the study, LDL-C levels were 48 mg/dl, 45 mg/dl, and 48 mg/dl for pravastatin, simvastatin, and simvastatin/ezetimibe groups, respectively (all, P<0.01 vs baseline). There was no significant difference among the treatment groups. The proportion of diabetic patients who attained LDL-C <70 mg/dL at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 40 mg once daily (dose could be increased to 80 mg if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin-ezetimibe 20/10 mg once daily (dose of simvastatin could be increased to 40 mg if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions)				end of the trial were 62%, 80%, and 78% for pravastatin, simvastatin, and simvastatin/ezetimibe groups, respectively (all, P=NS). There was no significant difference among the treatment groups. There were no significant differences in hs-CRP, HDL-C, TG among the treatment groups.
Crouse et al.[25] (2007) METEOR Rosuvastatin 40 mg once daily vs placebo	DB, RCT Adult patients between the ages of 45 and 70 years, with LDL-C between 120 and 190 mg/dL among patients whose only CHD risk factor was age, and an LDL-C between 120 and 160 mg/dL for individuals with ≥2	N=984 2 years	Primary: Annualized rate of change in maximum CIMT of the 12 carotid artery sites (near and far walls of the right and left common carotid artery, carotid bulb, and internal carotid artery)	Primary: Rosuvastatin therapy was associated with a significant reduction in the annualized rate of change in maximum CIMT from baseline compared with placebo (P<0.001). Secondary: Rosuvastatin therapy was associated with a statistically significant 49% reduction in LDL-C from baseline compared with placebo (P<0.001). Rosuvastatin therapy was associated with a statistically significant reduction in the annualized rate of change in the maximum CIMT for the common carotid artery sites (P<0.001), carotid bulb (P<0.001), and internal carotid artery sites (P=0.02) from baseline compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	CHD risk factors and a 10-year risk of CHD events of <10%, HDL-C level ≤60 mg/dL, level of TG <500 mg/dL, and maximum CIMT between 1.2 mm and 3.5 mm from 2 separate ultrasounds		Secondary: Annualized rate of change in maximum CIMT of the common carotid artery, carotid bulb, and internal carotid artery sites, and annualized rate of change in mean CIMT	Rosuvastatin therapy was associated with a statistically significant reduction in the annualized rate of change in the mean CIMT for the common carotid artery sites (P<0.001) from baseline compared with placebo.
Nissen et al.[26] (2006) ASTEROID Rosuvastatin 40 mg once daily	MC, OL, PRO Patients ≥18 years old, requiring coronary angiography for a stable or unstable ischemic chest pain syndrome or abnormal exercise test, with ≥1 obstruction ≥20% angiographic luminal diameter narrowing in a coronary vessel, not on statin therapy for >3 months within the last 12 months	N=507 24 months	Primary: Percent atheroma volume (PAV), absolute change in total atheroma volume (TAV) in the 10 mm subsegment of the coronary artery with the largest plaque volume at baseline Secondary: Change in normalized TAV, lipid parameters	Primary: With rosuvastatin treatment, patients experienced a significant reduction in PAV from baseline (–0.79%; 95% CI, –1.21% to –0.53%; P<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in atheroma volume in the most diseased 10 mm subsegment (–5.6 mm3; 95% CI, –6.82 mm3 to –3.96 mm3; P<0.001). Secondary: With rosuvastatin treatment, patients experienced a significant reduction from baseline in normalized TAV (–12.5 mm3; 95% CI, –15.08 mm3 to –10.48 mm3; P<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in the total normalized TAV (–6.8%; 95% CI, –7.82% to –5.60%; P<0.001). With rosuvastatin treatment, patients experienced a significant reduction from baseline in TC (33%), LDL-C (53.2%), TG (14.5%), LDL-C:HDL-C ratio (58.5%), and non–HDL-C (47.2%; P<0.001). With rosuvastatin treatment, patients experienced a significant increase from baseline in HDL-C (14.7%; P<0.001).
Chan et al.[178] (2010)	RCT, DB, PC	N=272	Primary: Hemodynamic	Primary: In the rosuvastatin group, the mean change in peak AS gradient was 18.3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ASTRONOMER Rosuvastatin 40 mg daily vs placebo	Patients 18-82 years of age with asymptomatic mild to moderate aortic stenosis (AS) defined by maximum aortic valve velocity between 2.5 and 4.0 m/s	Median 3.5 years	parameters of AS severity (transvalvular AS gradients and aortic valve area) Secondary: Composite of aortic valve replacement and cardiac death	mm Hg and the mean change in AS gradient was 10.7 mm Hg. The mean change in aortic valve area was -0.19 cm^2. In the placebo group, the mean change in peak AS gradient was 15.4 mm Hg and the mean change in AS gradient was 9.6 mm Hg. The mean change in aortic valve area was -0.16 cm^2. The mean changes in the peak AS gradient, mean gradient, and aortic valve area were not significantly different between the treatment groups (P=0.32, P=0.49, and P=0.79, respectively). Secondary: Cardiac death or aortic valve replacement events were not significantly different between the treatment groups (P=0.45).
Kastelein et al.[27] (2008) ENHANCE Simvastatin 80 mg daily and placebo vs simvastatin 80 mg daily and ezetimibe 10 mg daily	DB, MC, PRO, RCT Men and women between the ages of 30 and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without treatment	N=720 24 months	Primary Change in mean carotid artery IMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid	Primary: The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (P=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; P=0.92) or new plaque formation (2.8% vs 4.7%; P=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; P=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (P=0.93), carotid bulb (P=0.37), internal carotid artery (P=0.21) and femoral artery (P=0.16) or average of the mean values for carotid and femoral artery IMT (P=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	group difference of 16.5%; P<0.01). Reductions in TG (between-group difference of 6.6%; P<0.01) and CRP (between-group difference of 25.7%; P<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone. Adverse events (29.5% vs 34.2%; P=0.18) and discontinuation rates (9.4% vs 8.1%; P=0.56) were similar between simvastatin monotherapy and the combination therapy.
Rossebø et al.[188] (2008) SEAS Simvastatin 40 mg and ezetimibe 10 mg once daily vs placebo Open-label lipid-lowering therapy, which included up to 40 mg of simvastatin or an equipotent dose of another lipid-lowering drug, could be administered in addition to the study drug at the discretion of each treating physician	RCT, MC, DB Patients 45-85 years of age who had asymptomatic, mild-to-moderate aortic valve stenosis with a peak aortic-jet velocity of 2.5 to 4 m per second	N=1,873 Median 52.2 months	Primary: Composite of major cardiovascular events (death from cardiovascular causes, aortic-valve replacement, congestive heart failure as a result of progression of aortic-valve stenosis, nonfatal myocardial infarction, hospitalization for unstable angina, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or non-hemorrhagic stroke)	Primary: The composite of major cardiovascular events occurred in 35.3% of patients in the simvastatin/ezetimibe group and in 38.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.83 to 1.12; P=0.59). Secondary: There was no significant difference between the treatments in aortic-valve–related events (HR, 0.97; 95% CI, 0.83 to 1.14; P=0.73). Aortic-valve replacement occurred in 28.3% of patients in the simvastatin/ezetimibe group and in 29.9% of patients in the placebo group (HR, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Ischemic cardiovascular events occurred in 15.7% of patients in the simvastatin/ezetimibe group compared to 20.1% of patients in the placebo group (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.02). A total of 7.3% of patients in the simvastatin-ezetimibe group required CABG compared to 10.8% of patients in the placebo group (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.02). There was no significant difference in the progression of aortic stenosis between the treatment groups. The mean peak aortic jet velocity was 3.71 m per second in the placebo group compared to 3.69 m per second in the simvastatin/ezetimibe group at the end of the study (95% CI, −0.06 to 0.05; P=0.83). The mean pressure gradient increased to 34.4 mm Hg in the placebo group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Aortic-valve events, progression of aortic stenosis, safety	compared to 34.0±15.1 mm Hg in the simvastatin/ezetimibe group at the end of the study. There was no significant difference in the aortic-valve area between the treatment groups. There was no significant difference in overall mortality among the treatment groups (P=0.80). The composite outcome of death from cardiovascular causes and the individual components of this composite outcome did not differ significantly between the two groups (P=0.34). There was a significant increase in the number of patients with elevated liver enzyme levels in the simvastatin/ezetimibe group. There was also a higher incidence of cancer in the simvastatin/ezetimibe group (11.1%) compared to placebo (7.5%; P=0.01).
Adverse Events				
Zhao et al.[165] (2004) Simvastatin + niacin (S+N) vs placebo	RCT, PRO, DB, PC Patients with coronary artery disease and low HDL cholesterol. Diabetic patients were included if fasting glucose was ≤180 mg/dL.	N=160 3 years	Primary: Adverse effects	Primary: There were no statistically significant differences between S + N and placebo in terms of frequency of patients with side effects. Flushing of any severity was seen in 30% of patients in the S + N group and in 23% of the placebo group (P=0.35); severe flushing was 5% versus 0%, respectively. As compared with the placebo group, S + N did not significantly increase the number of patients with elevated aspartate aminotransferase (SGOT), CPK, uric acid, or homocysteine. LDL cholesterol levels <40 mg/dL were seen on ≥1 occasion in 22 of the S + N patients (28%) and none of the placebo group (P<0.001). Glycemic control for diabetic patients was more variable and slightly worse in the S + N group during the first few months of treatment, but by 8 months had returned to the pretreatment levels and remained stable for the rest of the study. Among 124 patients without diabetes or impaired fasting glucose (IFG) at baseline, 3 (2.4%) developed diabetes and 12 (9.7%) developed IFG. Both new diabetes and new IFG occurred more frequently in S + N group than in the placebo group, but the differences between the groups were not statistically significant.
Silva et al.[128] (2006)	MA	N=71,108 (18 trials)	Primary: Adverse events,	Primary: Statin therapy increased the risk of any adverse events by 39% compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Statins (atorvastatin, pravastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin) vs placebo	Randomized, prospective studies comparing statin therapy with placebo with a follow-up >6 weeks, reporting data on nonfatal adverse events	Up to 317 weeks	cardiovascular events	with placebo (OR, 1.4; 95% CI, 1.09 to 1.80; P=0.008). Consequently, out of 197 patients treated with statin therapy, one patient would experience an adverse event (95% CI, 24 to 37). Statin therapy was associated with a 26% reduction in the risk of a clinical cardiovascular event compared with placebo (OR, 0.74; 95% CI, 0.69 to 0.80; P<0.001). Consequently, the number needed-to-treat to prevent 1 additional cardiovascular event was 27. Rosuvastatin studies were not included in the analysis of cardiovascular risk reduction due to inadequate data. The incidence of adverse effects during statin administration was observed in the following order, from highest to lowest: atorvastatin >pravastatin=simvastatin= lovastatin>fluvastatin.
Kashani et al.[129] (2006) Statins (atorvastatin 20-80 mg, fluvastatin 2.5-80 mg, lovastatin 10-80 mg, pravastatin 10-160 mg, rosuvastatin 1-80 mg, simvastatin 2.5-80 mg) vs placebo	MA Randomized, double-blinded studies comparing statin therapy with placebo in adult patients (≥18 years of age) with hyperlipidemia, reporting data on adverse events; all studies were required to randomly allocate ≥100 patients to statin monotherapy vs placebo	N=74,102 (35 trials) Up to 65 months	Primary: Adverse events (myalgia, CK elevation, rhabdomyolysis, transaminase elevation), discontinuation due to adverse event; results expressed in terms of the risk difference (RD) per 100 patients	Primary: Statin therapy was not associated with a statistically significant increase in the risk of myalgias (RD, 2.7; 95% CI, –3.2 to 8.7; P=0.37), CK elevation (RD, 0.2; 95% CI, –0.6 to 0.9; P=0.64), rhabdomyolysis (RD, 0.4; 95% CI, –0.1 to 0.9; P=0.13), or discontinuation due to adverse events (RD, –0.5; 95% CI, –4.3 to 3.3; P=0.80) compared with placebo. Statin therapy was associated with a statistically significant risk of transaminase elevations (RD, 4.2; 95% CI, 1.5 to 6.9; P<0.01) compared with placebo. When individual statins were compared to placebo, atorvastatin was the only statin with a statistically significant increase in the risk of myalgias (P=0.04). When individual statins were compared to placebo, fluvastatin (P<0.01) and lovastatin (P=0.05) were the only statins with a statistically significant increase in the risk of transaminase elevation.
McClure et al.[130] (2007) Statins (atorvastatin, fluvastatin,	MA Randomized, controlled, double-blind studies comparing statin	N=86,000 (119 trials) Up to 65 months	Primary: Adverse events (myalgia, myositis, rhabdomyolysis), discontinuations due to adverse	Primary: Statin therapy was not associated with a statistically significant increase in the risk of myalgias (POR, 1.09; 95% CI, 0.97 to 1.23; P=0.471), rhabdomyolysis (POR, 1.59; 95% CI, 0.54 to 4.70; P=0.544), or myositis (POR, 2.56; 95% CI, 1.12 to 5.85; P=0.987) compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lovastatin, pravastatin, rosuvastatin, simvastatin), stratified by ≤40 mg and >40 mg daily lovastatin equivalent dose vs placebo	therapy with placebo in adult patients (≥18 years of age) with hyperlipidemia, reporting data on adverse events		events; results expressed in terms of Peto odds ratios (POR), in order to account for rare or zero events	Statin therapy was associated with a lower incidence of discontinuations due to adverse events (POR, 0.88; 95% CI, 0.84 to 0.93; P<0.001) compared with placebo.
Newman et al.[131] (2006) Atorvastatin 10 mg once daily vs atorvastatin 80 mg once daily vs placebo	MA Studies evaluating adverse effects of atorvastatin administered to patients with various cardiovascular risks, LDL-C level ≥130 mg/dL and triglyceride level ≤600 mg/dL	N=14,236 (42 trials) 2-52 months	Primary: Adverse effects	Primary: Treatment-related side effects were similar across all study groups. Treatment-associated myalgia was observed in 1.4%, 1.5%, and 0.7% of patients receiving atorvastatin 10 mg, 80 mg, and placebo, respectively. No cases of rhabdomyolysis were reported among the study groups. Elevations in hepatic transaminases >3 times the ULN were observed in 0.1%, 0.6%, and 0.2% of patients receiving atorvastatin 10 mg, 80 mg, and placebo, respectively.
Shepherd et al.[132] (2003) Rosuvastatin 5-40 mg once daily vs atorvastatin 10-80 mg once daily	MA Randomized, controlled studies comparing statin therapy with placebo or comparator statins in patients with dyslipidemia	N=16,876 (33 trials) 25,670 patient-years	Primary: Adverse events, elevation in transaminases, CK, myopathy, dipstick-positive proteinuria, estimated glomerular rate	Primary: The incidence of adverse events was similar in the rosuvastatin and the placebo groups (52.1% vs 51.8%, respectively). The incidence of adverse events was similar across all the active treatment groups. The incidence of elevation in transaminases, and CK, myopathy, dipstick-positive proteinuria, and estimated glomerular rate was similar across all the active treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs simvastatin 10-80 mg once daily vs pravastatin 10-40 mg once daily vs placebo once daily				
Dale et al.[133] (2007) Intensive-dose statin therapy including hydrophilic statins (atorvastatin 80 mg) and lipophilic statins (simvastatin 40-80 mg, lovastatin 76 mg) vs moderate-dose statin therapy including hydrophilic statins (atorvastatin 10 mg, pravastatin 40 mg) and lipophilic statins (simvastatin 20-40 mg, lovastatin 4 mg)	MA Randomized, comparative studies comparing intensive- and moderate-dose statin therapies in at least 100 patients, with a follow-up ≥48 weeks, reporting data on the incidence of elevations in AST, ALT or CK	N=21,765 (9 trials) Up to 5 years	Primary: Incidence of elevations in AST, ALT or CK	Primary: Intensive statin therapy was associated with an increased risk of AST, or ALT elevation, compared to the moderate-dose statin therapy (1.5% vs 0.4%; RR, 3.10; 95% CI, 1.72 to 5.58; P=0.002). Intensive statin therapy was not associated with a statistically significant risk of CK elevation, compared to the moderate-dose statin therapy (0.1% vs 0.02%; RR, 2.63; 95% CI, 0.88 to 7.85; P=0.89). In a subanalysis of hydrophilic and lipophilic statins, while no cases of CK elevation occurred in the hydrophilic intensive-dose statin group, patients on lipophilic intensive-dose statin therapy experienced a non–statistically significant risk in CK elevation (RR, 6.09; 95% CI, 1.36 to 27.35; P≥0.11).
Silva et al.[134] (2007)	MA	N=27,548 (4 trials)	Primary: CK ≥10 times the	Primary: Intensive statin therapy was associated with an increased risk of any

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Intensive-dose statin therapy (atorvastatin 80 mg, simvastatin 80 mg) vs moderate-dose statin therapy (atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg)	Randomized, comparative studies comparing intensive- and moderate-dose statin therapies for the reduction of secondary cardiovascular events in patients with ACS or stable CAD	3.4 years	ULN, with or without myalgia, ALT or AST ≥3 times the ULN, rhabdomyolysis, drug-induced adverse effects requiring drug discontinuation, any drug-induced adverse event, all-cause mortality, cardiovascular death, nonfatal MI, and stroke	adverse event compared with the moderate-dose statin therapy (OR, 1.44; 95% CI, 1.33 to 1.55; P<0.001). Consequently, out of 30 patients treated with intensive statin therapy, one patient would experience an adverse event (95% CI, 24 to 37). Intensive statin therapy was associated with an increased risk (absolute risk, 2.14%) of an adverse drug event requiring discontinuation of drug therapy (OR, 1.28; 95% CI, 1.18 to 1.39; P≤0.001). Intensive statin therapy was associated with an increased risk (absolute risk, 1.2%) of an elevation in AST/ALT ≥3 times the ULN (OR, 4.84; 95% CI, 3.27 to 6.16; P≤0.001). Consequently, out of 86 patients treated with intensive statin therapy, one patient would experience an elevation in AST/ALT ≥3 times the ULN (95% CI, 72 to 106). Intensive statin therapy was associated with an increased risk (absolute risk, 0.07%) of an elevation in CK ≥10 times the ULN (OR, 9.97; 95% CI, 1.28 to 77.92; P=0.028). Consequently, out of 1,534 patients treated with intensive statin therapy, one patient would experience an elevation in CK ≥10 times the ULN. There was no statistically significant difference in the incidence of rhabdomyolysis between the study groups. Intensive statin therapy was not associated with a significant reduction in all-cause mortality compared to the moderate-dose statin therapy (P=0.185). Intensive statin therapy was associated with a significant reduction in the risk for cardiovascular death (P=0.031), nonfatal MI (P<0.001), and stroke (P=0.004). Consequently, the number needed-to-treat to prevent 1 additional cardiovascular death, MI, or stroke was 229, 99, and 166, respectively.
Law et al.[135] (2006) Statins	MA Cohort studies, randomized, placebo-	21 trials Up to 6.1 years	Primary: Incidence of rhabdomyolysis, myopathy, renal	Primary: The incidence of rhabdomyolysis associated with the use of statins in two cohort and randomized, controlled studies was 3.4 (95% CI, 1.6 to 6.5) per 100,000 patient-years.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(lovastatin, atorvastatin, pravastatin, simvastatin, fluvastatin); doses were not reported vs placebo	controlled studies, voluntary adverse events notification to national regulatory authorities, and published individual case reports		failure, elevated ALT, renal failure, proteinuria, peripheral neuropathy	The incidence of rhabdomyolysis associated with the use of statins in addition to gemfibrozil in two cohort studies was 35 (95% CI, 1 to 194) per 100,000 patient-years. The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 4 times higher in patients receiving lovastatin, simvastatin, or atorvastatin compared with those on monotherapy with fluvastatin or pravastatin (P<0.001). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 15 times higher in patients receiving statins in combination with gemfibrozil (21 per 100,000 patient-years; 95% CI, 17 to 25) compared with those on statin monotherapy (0.70 per 100,000 patient-years; 95% CI, 0.62 to 0.79; P<0.001). The incidence of myopathy associated with the use of statins in randomized, controlled studies was 5 (95% CI, –17 to 27) per 100,000 patient-years. The incidence of liver failure associated with the use of statins, reported to the FDA adverse events reporting system, was 0.1 per 100,000 patient-years of use. Statin use in patients with elevated ALT would lead to liver disease in <1 person. Statin use was not associated with a higher incidence of renal failure or proteinuria than with placebo. Patients receiving statin therapy have 1.8 odds of experiencing peripheral neuropathy compared with placebo (95% CI, 1.1 to 3.0; P<0.001).
Cerebrovascular Disease				
The Stroke Prevention by Aggressive Reduction in Cholesterol Levels	RCT, DB, MC Patients ≥18 years of age who had had an ischemic or	N=4,731 Median 4.9 years	Primary: First nonfatal or fatal stroke Secondary:	Primary: First nonfatal or fatal stroke occurred in 265 patients in the atorvastatin group and 311 in the placebo group (P=0.05). After adjustment for baseline factors, atorvastatin was associated with a 16% reduction in the risk of nonfatal or fatal stroke (HR, 0.84; 95% CI, 0.71 to 0.99; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(SPARCL) Investigators[171] (2006) SPARCL Atorvastatin 80 mg daily vs placebo	hemorrhagic stroke or a TIA (diagnosed by a neurologist within 30 days after the event) 1 to 6 months before randomization. Patients with hemorrhagic stroke were included if they were deemed by the investigator to be at risk for ischemic stroke or coronary heart disease.		Stroke or TIA, major coronary event, major cardiovascular event, acute coronary event, any coronary event, revascularization procedure, and any cardiovascular event	Secondary: Atorvastatin reduced the risk of stroke or TIA (P<0.001), major coronary events (P=0.003), major cardiovascular events (P=0.002), acute coronary event (P=0.001), any coronary event (P<0.001), revascularization (P<0.001), and any cardiovascular event (P<0.001) compared to placebo. There was no significant difference between the treatment groups in overall mortality (P=0.98). There was no significant difference between the treatment groups in the incidence of serious adverse events. There were five cases of rhabdomyolysis (2 in the atorvastatin group and 3 in the placebo group). Elevation of alanine or aspartate aminotransferase (>3 times the upper limit of the normal) occurred more frequently in the atorvastatin group (2.2%) than in the placebo group (0.5%; P<0.001.

Study abbreviations: ARR=absolute risk reduction, CI=confidence interval, DB=double blind, DD=double dummy, ES=extension study, FU=follow-up, HR=hazard ratio, MA=meta-analysis, MC=multicenter, MN=multinational, I=international, OR=odds ratio, OL=open label, PC=placebo-controlled, PG=parallel group, POR=Peto odds ratio, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=risk ratio or relative risk, SB=single blind, SA=subanalysis
Miscellaneous abbreviations: ACS=acute coronary syndrome, ALT=alanine aminotransferase, ALT=alanine transaminase, AMI=acute myocardial infarction, apo AI=apolipoprotein AI, apo B=apolipoprotein B, apo E=apolipoprotein E, AST=aspartate aminotransferase, BMI=body mass index, BP=blood pressure, CABG=coronary artery bypass graft, CAC=coronary artery calcification, CAD=coronary artery disease, CCS=Canadian Cardiovascular Society, CDP=Coronary Drug Project, CHD=coronary heart disease, CIMT=carotid intima-media thickness, CK=creatine kinase, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, CVD=cardiovascular disease, CVD=cerebrovascular disease, ECG=electrocardiogram, FBG=fasting blood glucose, FPG=fasting plasma glucose, FSG=fasting serum glucose, GFR=glomerular filtration rate, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, hsCRP=high-sensitivity C-reactive protein, IMT=intima-medial thickness, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MACE=major adverse cardiac events, MI=myocardial infarction, NCEP=National Cholesterol Education Program, NCEP ATP III=National Cholesterol Education Program, Adult Treatment Panel III, NYHA=New York Heart Association, PAD=peripheral arterial disease, PAV=percent atheroma volume, PCI=percutaneous coronary intervention, TAV=total atheroma volume, TC=total cholesterol, TG=triglycerides, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein, VLDL-TG=very low-density lipoprotein triglycerides

Additional Evidence

Dose Simplification

Wongwiwatthananukit et al. evaluated the safety and efficacy with rosuvastatin 10 mg administered once-daily compared to every-other-day in patients with primary hypercholesterolemia.[139] There was a significantly larger reduction in LDL-C with once-daily therapy compared to every-other-day administration (48% vs 39%, respectively; P=0.011). Total cholesterol and triglycerides were significantly lower with once-daily therapy (P<0.05). However, there was no difference in the percentage of patients achieving their NCEP ATP III LDL-C goals (P=0.18).

LaFleur et al. evaluated the differences in adherence and persistence with (1) a fixed-dose combination product containing lovastatin and extended-release niacin, (2) statin monotherapy, (3) extended-release niacin monotherapy, and (4) extended-release niacin taken with lovastatin as separate formulations.[163] A total of 2,389 patients met the eligibility criteria and were followed for one year. All groups exhibited an adherence rate >80%. Patients receiving extended-release niacin and lovastatin taken separately demonstrated higher adherence rates compared to those on the fixed-dose product (90% vs 88%; P=0.033). In addition, patients were less adherent to statin monotherapy than to either the fixed-dose combination product or niacin monotherapy (81%, 90%, and 89%, respectively; P<0.05). At 12 months, all treatment groups had a persistence rate of <20%. At 9 months, patients randomized to niacin monotherapy exhibited a significantly lower rate of persistence compared to the rest of the groups (P<0.05). Since this was an adherence study only, based on an evaluation of pharmacy claims, the study did not measure the impact of adherence on low-density lipoprotein cholesterol (LDL-C) or other cholesterol goals.

Balu et al. retrospectively evaluated medication adherences rates in patients treated with the fixed-dose combination of niacin extended-release and lovastatin (NERL) compared to the multi-pill combination of niacin extended-release plus lovastatin (NER/L) or simvastatin (NER/S) using an integrated managed care database.[191] Adherence rates were greater among patients initiating therapy with NERL compared to NER/S or NER/L P<0.0001). A higher percentage of patients initiating therapy with NERL (34.2%) exhibited optimal adherence (>80%) compared to those initiating therapy with NER/S (29.6%; P<0.0001) or NER/L (25.9%; P<0.0001). There were fewer CVD-associated emergency room visits in patients with optimal adherence initiating therapy with NERL compared to those with optimal adherence initiating therapy with NER/S or NER/L (P=0.003), inpatient visits (P=0.018, outpatient visits (P<0.0001), and prescription fills (P<0.0001). Patients with optimal adherence had an 8% decrease (P=0.023) in annual CVD-attributable total medical resource utilization compared to patients with suboptimal adherence (<80%).

Patel et al. evaluated adherence rates in patients newly initiated on dual therapy with a calcium channel blocker and a statin (as either a fixed-dose combination product or administration of each component separately).[169] In this 6 month, retrospective, pharmacy claims database analysis, the authors found that the percentage of patients achieving adherence rates ≥80% were: 67.7% with amlodipine/atorvastatin; 49.9% with amlodipine and atorvastatin; 40.4% with amlodipine + other statins; 46.9% with other calcium channel blockers + atorvastatin; 37.4% with other calcium channel blocker + other statin (P<0.0001 amlodipine/atorvastatin vs all other cohorts).

Stable Therapy

Cheetham et al. evaluated the efficacy and safety of switching patients from Zocor® to generic lovastatin.[140] Patients switching to lovastatin experienced a reduction in LDL-C, an increase in HDL-C and a decrease in triglycerides. Rates of alanine aminotransferase and creatine kinase elevations were not found to be significantly different before or after conversion.

Usher-Smith et al. examined the effects of switching patients from atorvastatin to simvastatin in a 2-year retrospective analysis.[141] Patients initially receiving atorvastatin 10 mg and 20 mg were converted to simvastatin 10-20 mg or 40 mg, respectively. The change in therapy was not associated with a significant alteration in baseline total cholesterol levels (P=0.06).

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 HMG-CoA Reductase Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amlodipine and atorvastatin	tablet	Caduet®	$$$$	N/A
Atorvastatin	tablet	Lipitor®	$$$-$$$$	N/A
Ezetimibe and simvastatin	tablet	Vytorin®	$$$$	N/A
Fluvastatin	capsule, extended-release tablet	Lescol®, Lescol XL®	$$$-$$$$	N/A
Lovastatin	extended-release tablet, tablet	Altoprev®, Mevacor®*	$$$-$$$$	$
Niacin and lovastatin	extended-release tablet	Advicor®	$$$-$$$$	N/A
Niacin and simvastatin	extended-release tablet	Simcor®	$$$-$$$$	N/A
Pravastatin	tablet	Pravachol®*	$$$$	$
Rosuvastatin	tablet	Crestor®	$$$$	N/A
Simvastatin	tablet	Zocor®*	$$$$	$

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

X. Conclusions

The HMG-CoA reductase inhibitors (statins) are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia (refer to Table 4 for specific indications).[4-14] The fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/simvastatin, niacin/lovastatin and niacin/simvastatin) are indicated for use when dual therapy is appropriate. Statins can decrease LDL-C by 18% to 60% and triglycerides by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy.[17,20] Lovastatin, pravastatin and simvastatin are available in a generic formulation.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The statins are generally considered first-line therapy in addition to therapeutic lifestyle changes (TLC).[16-21] If the LDL-C goal is not achieved after 6 weeks of therapy, then the dose of the statin should be increased or another LDL-C lowering drug (such as niacin, a bile acid sequestrant or ezetimibe) should be added to the regimen. Guidelines do not give preference to one statin over another.

Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, total cholesterol and triglycerides, as well as positively impact other lipid/lipoprotein parameters.[22-127,143-162,164,166-168,170,172-190] Studies have also demonstrated that aggressive lipid-lowering with a statin allows patients to reach their NCEP ATP III LDL-C goals. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens. The statins differ in their potency and their effects on LDL-C are dose-dependent. Atorvastatin and rosuvastatin are the most potent agents available and can lower LDL-C by ~60%. However, most patients will likely not require this level of LDL-C reduction to achieve their individual goals of therapy. In general, the combination products do not offer any significant clinical advantage over coadministration of their individual components.

All of the statins have been shown to have beneficial effects on coronary heart disease (CHD) outcomes.[4-14,22-33,71-127,166,177-178,181-183,186-188] Atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin have been shown to reduce cardiovascular events in patients without CHD, but with multiple risk factors (primary prevention).[5,8,12-14] Atorvastatin, fluvastatin, pravastatin and simvastatin have also been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention).[5,7,12,14] In addition, fluvastatin, lovastatin, pravastatin and rosuvastatin have been shown to slow the progression of coronary atherosclerosis in patients with CHD.[7-8,13] Studies have demonstrated that statins (atorvastatin, pravastatin, rosuvastatin and simvastatin) also decrease the risk of stroke.[5,12-14,71,73-75,84-85,90,92,97,105-108,118,171,177] No incremental benefit of the combination products on cardiovascular morbidity and mortality has been established over and above that demonstrated for statin monotherapy.[4,6,10-11]

The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia and rash. Muscle aches and weakness are reported by 1-2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatine kinase. Pravastatin and rosuvastatin do not undergo extensive first-pass metabolism; therefore, they are associated with a lower risk for drug interactions.[1-3] Atorvastatin, lovastatin and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin is metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles (refer to Table 6).

There is insufficient evidence to support that one brand HMG-CoA reductase inhibitor is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand HMG-CoA reductase inhibitors 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 HMG-CoA reductase 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antilipemic Agents, Miscellaneous
AHFS Class 240692
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I. Overview

The antilipemic agents are categorized into 5 different AHFS classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their FDA-approved indications, mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Niacin and omega-3 acid ethyl esters are the only miscellaneous antilipemic agents that are included in this review. Niacin favorably affects all lipids and lipoproteins; however, the mechanism of action is not completely understood.[12] It may inhibit the mobilization of free fatty acids from adipose tissue, decrease the delivery of free fatty acids to the liver, decrease triglyceride synthesis, alter the hepatic production of apolipoprotein B, and increase HDL cholesterol (HDL-C) by reducing its catabolism.[7] Niacin can decrease LDL cholesterol (LDL-C) by 5% to 25% and triglycerides by 20% to 50%, as well as increase HDL-C by 15% to 35%.[12]

The mechanism by which omega-3 fatty acids decrease triglycerides (25% to 50%) and increase HDL-C is also not completely understood. It may be due to a reduction in triglyceride production and/or an increase in triglyceride clearance. LDL-C may increase when the triglycerides are lowered. Lovaza® is the only FDA-approved prescription omega-3 fatty acid product that is currently available for the treatment of hypertriglyceridemia. Each 1 g capsule contains at least 900 mg of ethyl esters of omega-3 fatty acids sourced from fish oil, which are predominantly eicosapentaenoic acid (EPA-approximately 465 mg) and docosahexaenoic acid (DHA-approximately 375 mg).[6] The total EPA and DHA dose recommended for triglyceride lowering is approximately 2 to 4 g per day.[8]

Over-the-counter niacin products are labeled as dietary supplements. While these supplements are "generally recognized as safe", the FDA does not examine the efficacy and safety of these products or regulate the manufacturing process.[8-9] The FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease". Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[9] The American Heart Association (AHA) states that "dietary supplement niacin must not be used as a substitute for prescription niacin" and "it should not be used for lowering cholesterol because of the potential for very serious side effects".[10]

The miscellaneous antilipemic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Niacin is available over-the-counter in a generic formulation. This class was last reviewed in May 2008.

Table 1. Antilipemic Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Niacin	extended-release tablet, sustained-release capsule*‡, sustained-release tablet*‡, tablet*‡	Niacor®, Niaspan®	niacin, Niacor®, Niaspan®
Omega-3 acid ethyl esters	capsule	Lovaza®	none

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antilipemic agents are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Antilipemic Agents, Miscellaneous

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[11] (2004)**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • In high-risk patients with high triglyceride (TG) or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and an LDL-lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (statins). The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report[12] (2002)**	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. • Initiate low-density lipoprotein-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. • If triglycerides are very high (≥500 mg/dL), triglyceride-lowering drugs (fibrate or nicotinic acid) become first line therapy. Nicotinic Acid • Nicotinic acid should be considered as a therapeutic option for higher risk persons with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Omega-3 Fatty Acids • Omega-3 fatty acids (linolenic acid, DHA, EPA) have 2 potential uses. • In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3-12 g/day have been used depending on tolerance and severity of

Clinical Guideline	Recommendation(s)
	hypertriglyceridemia. • Recent clinical trials also suggest that relatively high intakes of omega-3 fatty acids (1-2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive clinical trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1-2 g/day) for either primary or secondary prevention.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies**[13] **(2007)**	• Statins are first-line drugs for lowering LDL-C. • Niacin is considered an effective lipid-lowering agent, but flushing may limit use. • Niacin is more effective in increasing HDL-C than fibrates. • When triglycerides are between 450-900 mg/dL, either fibrates or statins may be used as first-line drugs, and niacin is considered a good drug for selected patients. • Fish oils are also triglyceride-lowering agents and might be useful as a third-line therapy for patients with hypertriglyceridemia resistant to or intolerant of fibrates or niacin or in combination with other triglyceride-lowering drugs.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update**[14] **(2006)**	<u>All Patients With Coronary and Other Atherosclerotic Vascular Disease</u> • In addition to other lifestyle modifications, increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day) for risk reduction is encouraged. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction. <u>Lipid Management</u> • Therapeutic options to reduce non–HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy. • Dietary supplement niacin must not be used as a substitute for prescription niacin.
Institute for Clinical Systems Improvement (ICSI): **Lipid Management in Adults**[15] **(2009)**	• For monotherapy, statins are the drugs of choice for lowering LDL. • If patients are unable to take statins, then bile-acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile-acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed. <u>Omega-3 Fatty Acids</u> • Lifestyle modifications may include fish oil (EPA and DHA). • The AHA recommends omega-3 fatty acids in patients with stable CAD and the recommended daily amount is 1 g of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish. • Dietary and non-dietary intake of omega-3 polyunsaturated fatty acids may reduce overall mortality and sudden death in patients with stable coronary artery disease.

Clinical Guideline	Recommendation(s)
	• For patients with high triglycerides (+/- elevated LDL-C), omega-3 fatty acids are a potential treatment option. Niacin • Niacin is considered a treatment option in patients with high LDL-C and high triglycerides (with or without low HDL-C). • Niacin is considered a treatment option in patients with high LDL-C (with or without low HDL-C). • Niacin is considered a treatment option in patients with isolated low HDL-C. • Niacin is considered a treatment option in patients with high triglycerides.
National Institute for Health and Clinical Excellence (NICE): **Lipid Modification**[16] **(2008)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a ≥20% 10-year risk of developing CVD. • Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for primary prevention. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of CVD. • Statin therapy is recommended for adults with clinical evidence of CVD. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dl) or LDL-C <2 mmol/L (<77 mg/dl) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association (AHA): Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: **A Scientific Statement From the American Heart Association**[54] **(2007)**	• Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
American Heart Association (AHA)/American Stroke Association (ASA): **Primary Prevention of Ischemic Stroke**[55] **(2006)**	• Patients with known CAD and high-risk hypertensive patients (even with normal LDL cholesterol levels) should be treated with lifestyle measures and a statin. • For patients with low HDL-C, consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL. • For patients with elevated Lp[a], consider niacin (immediate- or extended-release formulation) in conjunction with glycemic control and LDL-C control.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antilipemic agents 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 Antilipemic Agents, Miscellaneous[1-6]

Indication	Niacin Extended-Release†	Niacin Immediate-Release†	Omega-3 Acid Ethyl Esters†
Hypertriglyceridemia			
Adjunctive therapy for the treatment of adult patients with very high serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them*	✔	✔	
Adjunct to diet to reduce triglyceride levels in adults with severe (≥500 mg/dl) hypertriglyceridemia			✔
Primary Hypercholesterolemia and Mixed Dyslipidemia			
Adjunct to diet to reduce elevated total cholesterol, LDL cholesterol, Apo B and triglyceride levels, and to increase HDL cholesterol in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb)	✔		
Adjunct to diet for the reduction of elevated total cholesterol and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate (alone or in combination with a bile acid binding resin)		✔	
Reduce elevated total cholesterol and LDL cholesterol levels in adult patients with primary hyperlipidemia in combination with a bile acid binding resin	✔		
Treatment of primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb), in combination with simvastatin or lovastatin, when treatment with niacin, simvastatin, or lovastatin monotherapy is considered inadequate.	✔		
Secondary Prevention of Cardiovascular Disease			
Reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia	✔		
Slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia (in combination with a bile acid binding resin)	✔		

†Over-the-counter products are considered dietary supplements.
*Patients typically have serum triglyceride levels over 2000 mg/dL and have elevations of VLDL cholesterol as well as fasting chylomicrons. Patients who consistently have total serum or plasma triglycerides below 1000 mg/dL are unlikely to develop pancreatitis. Therapy with nicotinic acid may be considered for those patients with triglyceride elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antilipemic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antilipemic Agents, Miscellaneous[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Niacin	ER: 60-76	Not reported	Liver	ER: Renal (60-76) IR: Renal (88)	IR: 20-45 min
Omega-3 acid ethyl esters	Not reported	Not reported	Not reported	Not reported	Not reported

ER=extended-release, IR=immediate-release

V. Drug Interactions

There are no significant drug interactions reported with the miscellaneous antilipemic agents.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antilipemic agents are listed in Table 5. Pooled data from randomized, placebo-controlled trials have shown that prescription omega-3 acid ethyl esters are safe and well tolerated.[8] At usual antilipemic dosages, niacin is generally well tolerated and side effects are mild and transient.[2] The most common adverse effects with niacin are gastrointestinal upset, flushing and pruritus. Flushing is more common with the immediate-release formulation and may be diminished by starting with a low dose, taking niacin after meals, and by pretreating with aspirin or ibuprofen.[2] Sustained-release preparations have been shown to be hepatotoxic in doses ≥2 g per day. Cases of severe hepatic toxicity, including fulminant hepatic necrosis have occurred in patients who have substituted sustained-release niacin products for immediate-release products at equivalent doses.[4-5]

Table 5. Adverse Drug Events (%) Reported with the Antilipemic Agents, Miscellaneous[1-6]

Adverse Events	Niacin Extended-Release (Niaspan®)	Niacin Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters (Lovaza®)
Cardiovascular			
Angina pectoris	-	-	1
Arrhythmia	✔	✔	✔
Atrial fibrillation	✔	✔	-
Bypass surgery	-	-	✔
Cardiac arrest	-	-	✔
Chest pain	-	-	✔
Hypertension	-	-	✔
Hypotension	✔	✔	-
Migraine	✔	-	✔
Myocardial infarction	-	-	✔
Myocardial ischemia	-	-	✔
Occlusion	-	-	✔
Orthostasis	✔	✔	-
Palpitations	✔	-	-
Peripheral edema	✔	-	-
Peripheral vascular disorder	-	-	✔
Postural hypotension	✔	-	-

Adverse Events	Niacin Extended-Release (Niaspan®)	Niacin Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters (Lovaza®)
Syncope	✔	-	✔
Tachycardia	✔	-	✔
Central Nervous System			
Depression	-	-	✔
Dizziness	✔	-	✔
Emotional lability	-	-	✔
Facial paralysis	-	-	✔
Headache	-	✔	-
Insomnia	✔	-	✔
Migraine	✔	-	-
Nervousness	✔	-	-
Paresthesia	✔	-	-
Vasodilatation	-	-	✔
Vertigo	-	-	✔
Dermatologic			
Acanthosis nigricans	-	✔	-
Alopecia	-	-	✔
Dry skin	✔	✔	-
Eczema	-	-	✔
Flushing	63-69	✔	-
Hyperpigmentation	-	✔	-
Pruritus	3-8	✔	✔
Rash	0-5	-	2
Urticaria	✔	-	-
Skin burning sensation	✔	-	-
Skin discoloration	✔	-	-
Sweating	✔	-	✔
Endocrine and Metabolic			
Gout	✔	✔	-
Gastrointestinal			
Abdomen enlarged	-	-	✔
Anorexia	-	-	✔
Colitis	-	-	✔
Constipation	-	-	✔
Diarrhea	7-14	✔	-
Dry mouth	-	-	✔
Dyspepsia	-	✔	3
Dysphagia	-	-	✔
Eructation	✔	-	5
Fecal incontinence	-	-	✔
Flatulence	✔	-	-
Gastritis	-	-	✔
Gastroenteritis	-	-	✔
Increased appetite	-	-	✔
Intestinal obstruction	-	-	✔
Melena	-	-	✔
Nausea	4-11	-	-
Pancreatitis	-	-	✔
Peptic ulceration	✔	✔	-
Tenesmus	-	-	✔
Vomiting	0-9	✔	✔
Hematologic			

Adverse Events	Niacin Extended-Release (Niaspan®)	Niacin Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters (Lovaza®)
Prothrombin time increased	✔	-	-
Thrombocytopenia	✔	-	-
Hepatic			
Fulminant hepatic necrosis	-	✔	-
Hepatitis	✔	-	-
Hepatotoxicity	✔	✔	-
Jaundice	✔	✔	-
Laboratory Test Abnormalities			
Amylase increased	✔	-	-
Hyperglycemia	✔	✔	✔
Hyperlipidemia	-	-	✔
Hyperuricemia	✔	✔	-
Lactate dehydrogenase increased	✔	-	-
Liver function test abnormalities	✔	✔	✔
Phosphorus decreased	✔	-	-
Musculoskeletal			
Arthralgia	-	-	✔
Arthritis	-	-	✔
Asthenia	✔	-	✔
Back pain	-	-	2
Fracture	-	-	✔
Malaise	-	-	✔
Myalgia	✔	-	✔
Myasthenia	✔	-	-
Myopathy	✔	-	-
Neck pain	-	-	✔
Pain	-	-	2
Rhabdomyolysis	-	✔	-
Rheumatoid arthritis	-	-	✔
Tendon rupture	-	-	✔
Respiratory			
Asthma	-	-	✔
Bronchitis	-	-	✔
Cough	2-8	-	✔
Dyspnea	✔	-	✔
Epistaxis	-	-	✔
Laryngitis	-	-	✔
Pharyngitis	-	-	✔
Pneumonia	-	-	✔
Rhinitis	-	-	✔
Sinusitis	-	-	✔
Urogenital			
Cervix disorder	-	-	✔
Endometrial carcinoma	-	-	✔
Epididymitis	-	-	✔
Impotence	-	-	✔
Other			
Anaphylaxis	✔	-	✔
Angioedema	✔	-	-
Blurred vision	✔	-	-
Body odor	-	-	✔
Cataract	-	-	✔

Adverse Events	Niacin Extended-Release (Niaspan®)	Niacin Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters (Lovaza®)
Chills	-	-	✔
Edema	-	-	✔
Facial edema	✔	-	-
Fever	-	-	✔
Flu symptoms	-	-	4
Hemorrhagic diathesis	-	-	✔
Hypersensitivity reactions	✔	-	-
Infection	-	-	4
Laryngismus	✔	-	-
Larynx edema	✔	-	-
Lymphadenopathy	-	-	✔
Macular edema	✔	✔	-
Neoplasm	-	-	✔
Sudden death	-	-	✔
Suicide	-	-	✔
Taste perversion	-	-	3
Tongue edema	✔	-	-
Toxoid amblyopia	-	✔	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antilipemic agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the Antilipemic Agents, Miscellaneous[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Niacin	Dyslipidemia: Tablet (IR): Initial, 250 mg once daily following the evening meal; increase every 4-7 days to desired response or the first-level therapeutic dose of 1.5 to 2 g/day is reached. After 2 months, the dose may be increased at 2- to 4-week intervals to 3 g/day (1 g three times per day). Maximum, 6 g/day Tablet (SR): Initial, 500 mg at bedtime for 4 weeks, then 1 g at bedtime for 4 weeks; after week 8, titrate to patient response and tolerance; can increase to a maximum of 2 g/day, but only at 500 mg/day at 4-week intervals Concomitant Therapy with Lovastatin or Simvastatin: Tablet (SR): Patients already	Safety and effectiveness in children have not been established.	Capsule (SR): 250 mg 500 mg Tablet (IR): 50 mg 100 mg 250 mg 500 mg Tablet (SR): 250 mg 500 mg 750 mg 1,000 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	receiving a stable dose of lovastatin or simvastatin who require further TG-lowering or HDL-raising may receive concomitant dosage titration with niacin SR per the recommended initial titration schedule. For patients already receiving a stable dose of niacin SR who require further LDL-lowering, the usual recommended starting dose of lovastatin and simvastatin is 20 mg once daily. Dose adjustments should be made at intervals of 4 weeks or more. Combination therapy with niacin SR and lovastatin or niacin SR and simvastatin should not exceed doses of 2,000 mg niacin SR and 40 mg lovastatin or simvastatin daily.		
Omega-3 acid ethyl esters	Hypertriglyceridemia: 4 g/day taken as a single 4 g dose or as two 2 g doses (2 capsules given twice daily)	Safety and effectiveness in children have not been established.	Capsule: 1 g

IR=immediate-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antilipemic agents are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Antilipemic Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Elam et al.[24] (2000) Niacin IR (Niacor®) 3,000 mg per day or maximum tolerated dosage vs placebo	MC, PC, RCT Patients with peripheral arterial disease with or without diabetes, mean age 67 years for patients with diabetes and 65 years for those without diabetes	N=468 (N=125 patients with diabetes) Up to 60 weeks (12-week active run-in and 48-week double-blind)	Primary: Change in lipid profile, glucose, A1C, ALT, uric acid; hypoglycemic drug use, compliance, adverse events	Primary: Niacin use significantly increased HDL-C by 29% and 29% and decreased TG by 23% and 28% and LDL-C by 8% and 9%, respectively, in participants with and without diabetes compared to baseline (P<0.001 for niacin vs placebo for all). Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL; P=0.04 and P<0.001) in participants with and without diabetes, respectively. A1C levels were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, A1C decreased by 0.3% (P=0.04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo.
Grundy et al.[25] (2002) Niacin ER (Niaspan®) 1,000 mg per day vs niacin ER (Niaspan®) 1,500 mg per day vs	DB, PC, RCT Patients with stable type 2 diabetes, 47% were receiving concomitant statin therapy	N=148 16 weeks	Primary: Change in HDL-C, TG, A1C Secondary: TC, LDL-C, FBG, adverse effects	Primary: Dose-dependent increases in HDL-C (13% to 19% for the 1,000 mg dose and 22% to 24% for the 1,500 mg dose; both P<0.05 vs placebo) and reductions in TG levels (–15% to –20% for the 1,000 mg dose; P=NS, and –28% to –36% for the 1,500 mg dose; P<0.05) were observed. Changes in A1C levels from baseline to week 16 were no different for niacin 1,000 mg/day (7.28% and 7.35%; P=0.16) and placebo (7.13% and 7.11%) but were significantly different for niacin 1,500 mg/day (7.2% and 7.5%; P=0.048). Secondary: Mean LDL-C levels were not significantly different than baseline for the placebo and niacin 1,000 mg groups. In the niacin 1,500 mg group, LDL-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				C levels decreased at all time points and the difference vs placebo was statistically significant at weeks 12 and 16 (P<0.05). The mean changes from baseline at 16 weeks were +9%, +5% and –7% in the placebo, niacin 1,000 mg and 1,500 mg groups, respectively. Similar trends were observed for TC with mean increases of +4% in both the placebo and niacin 1,000 mg groups and a decrease of –6% in the niacin ER 1,500 mg group. In both the niacin groups, an initial rise in FBG was observed between weeks 4 and 8 which returned to baseline by week 16. Four patients in the niacin group (3 patients were receiving 1,500 mg) discontinued participation because of inadequate glucose control. Rates of adverse events other than flushing were similar for the niacin and placebo groups. Flushing was reported by about 67% of patients receiving niacin ER and about 10% of patients receiving placebo. Four patients, including 1 patient in the placebo arm, withdrew from the study due to flushing. No hepatotoxic effects or myopathy was observed.
Kuvin et al.[26] (2006) Niacin ER (Niaspan®) initially 500 mg HS for 2 weeks then 1,000 mg HS vs placebo	PC, RCT Patients with stable coronary artery disease and LDL-C <100 mg/dL, all received concurrent statin therapy (>80% atorvastatin)	N=60 3 months	Primary: Changes in lipoproteins, HDL and LDL particle distribution and inflammatory markers	Primary: Six patients did not complete the protocol, 2 discontinued treatment due to flushing and 4 were lost to follow-up. Niacin significantly increased total HDL-C by 7.5% and decreased TG by 15% compared to baseline (P<0.005 for both), whereas TC and LDL-C remained unchanged. Compared with baseline values, the addition of niacin resulted in a 32% increase in large-particle HDL (P<0.001) and an 8% decrease in small-particle HDL (P=0.0032). Addition of niacin produced an 82% increase in large-particle LDL (P=0.09) and a 12% decrease in small-particle LDL (P=0.008). Niacin also favorably altered inflammatory markers with lipoprotein-associated phospholipase A2 and CRP levels decreasing by 20% and 15%, respectively, compared to baseline (P<0.05 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant changes from baseline were seen in any tested parameter in patients who received placebo. No major cardiovascular events were reported during the study in the treatment or placebo group.
Capuzzi et al.[27] (1998) Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction.	ES, MC, OL Patients with primary hypercholesterolemia who were previously enrolled in a randomized short-term study or in a placebo-only qualification clinical trial	N=517 Up to 96 weeks	Primary: Changes in LDL-C and apo B Secondary: Changes in TC, HDL-C, TC:HDL-C ratio, Lp(a) and TG; adverse events	Primary: Patients receiving niacin experienced significant reductions in LDL-C by 18% at week 48 and 20% at week 96. Similar reductions were seen with apo B (16% at week 48 and 19% at week 96). The percent changes achieved by both 48 and 96 weeks of therapy were statistically significant (P<0.001). Secondary: HDL-C significantly increased by 26% at week 48 and 28% at week 96 in patients receiving niacin. TC modestly decreased (12% and 13%, respectively), whereas the TC:HDL-C ratio decreased by almost one third (all P<0.001). TG and Lp(a) levels were decreased by 27% and 30%, respectively, at week 48, and by 28% and 40%, respectively, at week 96 (all P<0.001). Niacin was generally well tolerated. Flushing was common (75%); however, there was a progressive decrease in flushing with time from 3.3 episodes in the first month to ≤1 episode by week 48. Aspirin was used by one third of patients before niacin dosing to minimize flushing episodes. Six percent of patients discontinued therapy due to flushing. Serious adverse events occurred in about 10% of patients; however, none were considered probably or definitely related to niacin. No deaths or myopathy occurred. There were statistically significant increases in alkaline phosphatase, ALT, amylase, AST, direct bilirubin, glucose, and uric acid and a decrease in phosphorus (all P<0.001). Mean platelet counts decreased by 10.1% at week 48 and 14.8% at week 96, whereas leukocyte counts increased by 6.5% and 6.8%, respectively, at week 48 and week 96 of therapy (all P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Guyton et al.[28] (1998) Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction.	ES, MC, OL Patients with primary hyperlipidemia who were previously enrolled in an RCT or in a placebo-only qualification clinical trial	N=269 patients treated up to 96 weeks and a cohort of N=230 patients treated for 3 months (safety data)	Primary: Changes in TC, LDL-C, HCL-C, TG, apo B and Lp(a); safety	Primary: The dosages of niacin attained by 269 patients were 1,000 mg (95% of patients), 1,500 mg (86%) and 2,000 mg (65%). After 96 weeks of treatment, niacin alone (median dose 2,000 mg) significantly reduced LDL-C (18%), TC (10%), and TG (26%) and increased HDL-C (32%). Apo B and Lp(a) were significantly reduced by 26% and 36%, respectively, at 48 weeks but values for these parameters were not available at 96 weeks (P<0.01 for all values). At 96 weeks of the study, niacin plus a statin significantly lowered LDL-C (32%), TC (24%) and TG (32%) and increased HDL-C (25%) (P<0.01 for all values). Apo B (26%; P<0.01) and Lp(a) (19%; P=NS) were also reduced at 48 weeks but values for these parameters were not available at 96 weeks. Niacin plus a bile acid sequestrant lowered LDL-C (28%) and TC (15%) and increased HDL-C (31%) (P<0.01 for all values). Niacin plus a bile acid sequestrant increased TG (5%; P=NS). Apo B and Lp(a) were significantly reduced by 19% and 24% (P<0.01), respectively, at 48 weeks but values for these parameters were not available at 96 weeks. Intolerance to flushing led 4.8% of participants (13 of 269) to discontinue niacin. (Combining all of the data, 7.3% of patients discontinued niacin due to flushing.) Other medication-related adverse events leading to discontinuation from the 96-week study included nausea (3.3% of patients) sometimes with vomiting, other gastrointestinal symptoms (1.5%) and pruritus (2.6%). One case each of acanthosis nigricans, elevated glucose, gout, headache, palpitations and shoulder pain led to patient withdrawal. Overall, 9 of 499 (2.6%) patients experienced an ALT or AST elevation >2 times ULN. Five of these patients were on combination therapy, including 4 with a statin and 1 with a bile acid sequestrant. In 5 of the 9 cases, the transaminase elevation resolved while niacin was continued without reduction in dose. Three cases led to niacin dosage reduction. One patient discontinued niacin because of transaminase elevations. Leg aches

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and myalgias with normal creatine kinase levels were described in 1 patient taking niacin with simvastatin.
Gray et al.[29] (1994) Niacin SR (Slo-Niacin®) average maintenance dose of 1.67 g per day	RETRO Male veterans with dyslipoproteinemia who were treated with niacin	N=969 1-36 months	Primary: Changes in lipid profile, alterations in hepatic enzymes and blood chemistry tests, hepatotoxicity	Primary: Lipoprotein responses were dose-related and favorable. Results included the following: TC –19.1%, LDL-C –24.0%, HDL-C +5.7%, and TG –32.5% (all P≤0.0035). Statistically but not clinically meaningful dose-related increases were seen in levels of liver enzymes and serum glucose (AST +29%, ALT +23%, alkaline phosphatase +25%, and glucose +7%; P=0.0001). Niacin was discontinued in 48.5% (435 of 896) of patients primarily because of adverse effects. The primary documented reasons for discontinuation included flushing and itching (8.9%), increased serum glucose (4.8%), gastrointestinal complaints (3.7%) and increased liver function tests (3.7%). Poor glycemic control led to discontinuation in 40.6% (43 of 106) patients with diabetes mellitus. Twenty of 896 (2.2%) and 42 of 896 (4.7%) patients met biochemical criteria for “probable” and for “possible or probable” niacin-induced hepatotoxicity, respectively. Predisposing factors included high dose, alcohol use, preexisting liver disease and concurrent oral sulfonylurea therapy.
Knopp et al.[30] (1998) Niacin IR titrated to 3 g per day vs niacin ER (Niaspan®) titrated to 1.5 g per day vs	DB, MC, PG, RCT Patients with hypercholesterolemia, average age 54 years	N=223 25 weeks (9 week lead-in period)	Primary: Change in LDL-C, FPG, uric acid, drug tolerance Secondary: Change in TC, TG, HDL-C, HDL sub-fractions, apo B, apo AI, apo E, and Lp(a)	Primary: LDL-C was significantly reduced by 12%, 12% and 22%, respectively, by niacin ER 1.5 g HS, niacin IR 1.5 g/day, and niacin IR 3.0 g/day, respectively, compared to placebo (P≤0.05). At equal doses of 1.5 g/day of niacin ER versus niacin IR, AST increased 5.0% vs 4.8% (P=NS), FPG increased 4.8% vs 4.5% (P=NS), and uric acid concentration increased 6% vs 16% (P=0.0001), respectively. Flushing events were more frequent with niacin IR versus niacin ER (1,905 vs 575; P<0.001). Flushing severity was slightly greater with SR niacin, but still well tolerated. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				Compared with placebo at 8 weeks, niacin SR 1.5 g HS vs niacin IR 1.5 g/day showed comparable efficacy in lowering TC, TG, apo B, apo E and Lp(a), and raising HDL-C, HDL2-C, HDL3-C and apo AI (P≤0.05 in all instances). Niacin IR 3.0 g/day produced significantly greater changes in the above lipid parameters compared to niacin IR 1.5 g/day and niacin ER 1.5 g HS (P≤0.05).
McKenney et al.[31] (1994) Niacin IR administered BID at daily doses of 500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 3,000 mg, each for 6 weeks vs Niacin SR administered BID at daily doses of 500 mg, 1,000 mg, 1,500 mg, 2,000 mg, and 3,000 mg, each for 6 weeks	DB, PG, RCT Patients with LDL-C >160 mg/dL after 1 month on an NCEP ATP III - Step 1 diet	N=46 36 weeks	Primary: LCL-C, HDL-C, TG, adverse events (especially hepatotoxicity)	Primary: Niacin SR lowered LDL-C significantly more than niacin IR at the dosage of 1,500 mg/day and above (P<0.04 to P<0.001). Niacin IR increased HDL-C levels significantly more than niacin SR at all dosage levels (P<0.04 to P<0.001). The reduction in TG levels was similar (P=NS) between IR and SR niacin at all dosages except for the 1,000 mg dose where the IR formulation led to significantly greater reductions (P=0.009). Nine of 23 patients (39%) in the niacin IR group withdrew before completing the 3,000 mg daily dose. Four patients withdrew at the 1,000 mg dose, 1 patient at the 1,500 mg dose, 3 patients at the 2,000 mg dose and 1 patient at the 3,000 mg dose. The most common reasons for withdrawal were vasodilatory symptoms, fatigue, and acanthosis nigricans. Eighteen of 23 patients (78%) in the niacin SR group withdrew before completing the 3,000 mg daily dose. Two patients withdrew at the 1,000 mg dose, 2 patients at the 1,500 mg dose, 7 patients at the 2,000 mg dose and 7 patients at the 3,000 mg dose. The most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in liver function tests, often with symptoms of hepatic dysfunction. None of the patients taking niacin IR developed hepatotoxic effects, while 12 patients (52%) receiving niacin SR did.
Superko et al.[32] (2004)	PC, RCT	N=218	Primary: Changes in lipid	Primary: Treatment with niacin IR and ER significantly decreased TG, LDL-C, apo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Niacin IR 3 g per day vs Niacin ER (Niaspan®) 1.5 g per day vs placebo	Patients with hypercholesterolemia	14 weeks	profile and lipoprotein subclass distribution	B, and Lp(a) and significantly increased HDL-C (all P≤0.0001). Both niacin products significantly increased mean LDL peak particle diameter and percent distribution of large LDL I and IIa, with a significant decrease in small LDL IIIa, IIIb, and IVb (all P<0.05 with the exception of LDL I where P=0.12 for SR niacin 1,500 mg). In general, the effects were greater in patients with LDL pattern B (predominance of dense LDL) compared with those with LDL pattern A (predominance of buoyant LDL). Compared to the niacin IR 3,000 mg group, niacin ER 3,000 mg produced a smaller decrease in TG (–27% vs –47%; P<0.001) but had similar changes in LDL-C (–20% vs –22%), apo B (–22% vs –21%), HDL-C (27% vs 28%) and LDL peak particle diameter (0.90 mm vs 0.76 mm).
Alrasadi et al.[47] (2008) Protocol 1 Niacin ER 1 g twice daily for 8 weeks vs fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks Protocol 2 Niacin ER 1 g	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC/HDL-C ratio	Primary: Protocol 1 The mean percent change in HDL-C was +6%, -6%, and +22% in patients receiving fenofibrate, atorvastatin and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19%, -26% and -22% in patients receiving fenofibrate, atorvastatin and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). Protocol 2 The mean percent change in HDL-C was -2% and +18% in patients receiving fenofibrate + atorvastatin and niacin + atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +32% and -32% in patients receiving fenofibrate + atorvastatin and niacin + atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC/HDL-C (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
twice daily and atorvastatin 20 mg/day for 8 weeks vs fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2				
Guyton et al.[33] (2000) Niacin ER (Niaspan®) titrated up to 1 g for 4 weeks, 1.5 g for 4 weeks and 2 g for 8 weeks vs gemfibrozil 600 mg BID	DB, MC, PC, RCT Patients between the ages of 21 and 75 years with an HDL-C ≤40 mg/dL, LDL-C ≤160 mg/dL or <130 mg/dL with atherosclerotic disease, TG ≤400 mg/dL	N=173 8 weeks	Primary: Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	Primary: Niacin ER 1,500 mg and 2,000 mg raised HDL-C by 21% and 26%, respectively, vs 13% with gemfibrozil (P<0.02). Secondary: Niacin ER 1,500 mg and 2,000 mg vs gemfibrozil significantly raised apo AI (9% and 11% vs 4%), reduced TC:HDL-C ratio (–17% and –22% vs –12%), reduced Lp(a) level (–7% and –20% vs no change), and had no adverse effect on LDL-C (2% and 0% change vs 9% increase; P values ranged from P<0.001 to P<0.02.). Triglycerides decreased by 40% with gemfibrozil vs 16% with niacin ER 1,000 mg (P<0.001) and 29% with niacin 2,000 mg (P<0.06). Effects on plasma fibrinogen levels were significantly favorable for niacin ER compared with gemfibrozil (–1% to –6% vs 5% to 9%, respectively; P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Flushing was significantly more frequent with niacin ER (78% of patients) compared with gemfibrozil (10% of patients) at every point. Flu syndrome occurred more frequently with niacin ER vs gemfibrozil group (P=0.006). Dyspepsia was a more frequent occurrence with gemfibrozil (P=0.009).
Guyton et al.[52] (2008) Niacin ER 2 g (titrated) per day and ezetimibe-simvastatin (E/S) 10/20 mg once daily vs niacin ER 2 g (titrated) per day vs ezetimibe-simvastatin (E/S) 10/20 mg once daily	RCT, DB, MC Patients 18 to 79 years of age with type IIa and IIb hyperlipidemia (LDL-C 130 to 190 mg/dl and TG ≤500 mg/dl)	N=1,220 24 weeks	Primary: Percent change from baseline in LDL-C, non-HDL-C, HDL-C, TG, TC, apo B, apo A-I, and high-sensitivity C-reactive protein (hsCRP)	Primary: After 24 weeks of therapy, the percent change from baseline in LDL-C, non–HDL-C, TG, ApoB, TC/HDL-C, LDL-C/HDL-C, ApoB/ApoA-I, and non–HDL-C/HDL-C were greater with niacin + E/S compared to treatment with niacin or E/S (all P<0.001). The percent change in HDL-C from baseline was significantly greater with niacin + E/S compared to E/S (P<0.001). There was no significant difference with niacin + E/S and niacin monotherapy (P>0.05). The percent change in TC from baseline was significantly greater with niacin + E/S compared to niacin (P<0.001). There was no significant difference with niacin + E/S and E/S monotherapy. The percent change in ApoA-I from baseline was significantly greater with niacin + E/S compared E/S (P<0.001). There was no significant difference with niacin + E/S and niacin monotherapy (P>0.05). Treatment with niacin + E/S led to a greater reduction in hsCRP compared to niacin monotherapy (P<0.005). Adverse events occurred more frequently in patients treated with niacin monotherapy and niacin + E/S compared to E/S monotherapy. This difference was due to flushing-related AEs in the niacin groups.
Fazio et al.[53] (2010) Niacin ER 2 g (titrated) per day and ezetimibe-simvastatin (E/S) 10/20 mg once	RCT, DB, MC, ES Patients 18 to 79 years of age with type IIa and IIb hyperlipidemia (LDL-C 130 to 190 mg/dl and TG ≤500	N=942 64 weeks	Primary: Safety and tolerability Secondary: Percent change from baseline in HDL-C, TG, non-	Primary: After 64 weeks of treatment, clinical adverse events (AEs) occurred in 82.4% of patients receiving niacin + E/S compared to 76.5% of patients receiving E/S (95% CI, 0.3 to 11.9). Laboratory AEs were similar between the treatment groups (7.6% vs 10.7%, respectively; 95% CI, -7.6 to 0.8). A significantly greater percentage of patients receiving niacin + E/S

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs ezetimibe-simvastatin (E/S) 10/20 mg once daily	mg/dl)		HDL-C, LDL-C, other lipids, lipoprotein ratios and high-sensitivity C-reactive protein (hsCRP)	(26.4%) discontinued therapy due to flushing compared to those taking E/S (13.2%; 95% CI, 7.6 to 18.1). Increased fasting glucose occurred in 2.9% of patients receiving E/S compared to 1.6% in the niacin + E/S group. A similar number of patients in both groups had a worsening of diabetes. Secondary: After 64 weeks of therapy, treatment with niacin + E/S led to a significant improvement in HDL-C, TG, non-HDL-C, LDL-C, ApoB, ApoA-I, and lipoprotein ratios compared to E/S (P≤0.004). There was no significant difference in TC among the treatment groups. There was no significant difference in hsCRP among the treatment groups after 64 weeks of therapy.
Zhao et al.[22] (2004) Niacin SR (Slo-Niacin®) titrated to 1 g twice daily and simvastatin vs antioxidants vs niacin SR (Slo-Niacin®) titrated to 1 g twice daily, simvastatin, and antioxidants	ES Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) including 25 with diabetes mellitus with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	N=160 38 months	Primary: Side effects, response to question "Overall, how difficult is it to take the study medication?"	Primary: Patients who had received niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo: any degree of flushing (30% vs 23%; P=NS), symptoms of fatigue, nausea and/or muscle aches (9% vs 5%; P=NS), AST ≥3 times ULN (3% vs 1%; P=NS), CPK ≥2 times ULN (3% vs 4%; P=NS), new onset of uric acid ≥7.5 mg/dL (18% vs 15%; P=NS), and homocysteine ≥15 µmol/L (9% vs 4%; P=NS). There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly in the niacin plus simvastatin group but returned to pretreatment levels at 8 months and remained stable for the rest of the study. The niacin plus simvastatin combination regimen was repeatedly described by 91% of treated patients and 86% of placebo patients as "very easy" or "fairly easy" to take.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.				
Pownall et al[35] (1999) Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, PG, RCT Patients with severe hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks	Primary: Effect on TG, lipid profile, and lipid composition	Primary: Median TG levels were reduced 38.9% from baseline in the omega-3 acid ethyl ester group compared to 7.8% with placebo (P=0.001). Omega-3 acid ethyl esters also significantly reduced TC (–9.9%; P=0.004) and VLDL-C (–29.2%; P=0.001) and significantly increased LDL-C (16.7%; P=0.007) from baseline. HDL-C increased in patients receiving omega-3 acid ethyl esters (5.9%; P=0.057 vs baseline and P=0.023 vs placebo) and decreased in patients receiving placebo (–5.9%; P=NS vs baseline).
McKeone et al.[36] (1997) Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, RCT Patients with severe hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks	Primary: Effect on TG and serum phospha-tidylcholine Secondary: Changes in lipid profile	Primary: Treatment with omega-3 acid ethyl esters significantly reduced TG levels by 26% compared to a 7% increase for placebo. Incorporation of eicosapentaenoic and docosahexaenoic acid into the serum phosphatidylcholine occurred within 6 weeks and was usually accompanied by a reduction in plasma TG. Secondary: Omega-3 acid ethyl esters also significantly reduced VLDL-C (28%) and TC (11%), and increased HDL-C (14%). None of these parameters significantly changed in the placebo group.
Calabresi et al.[37]	DB, RCT, XO	N=14	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2000) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks vs placebo for 8 weeks	Patients with familial combined hyperlipidemia	26 weeks	Changes in lipid profile and LDL-C subclass distribution Secondary: Safety	Omega-3 acid ethyl esters significantly lowered plasma TG and VLDL-C by 27% and 18%, respectively (both P<0.05) compared to baseline. TC and HDL-C did not change but LDL-C and apo B increased by 21% (P=0.05) and 6% compared to baseline (P<0.05). Omega-3 acid ethyl esters treatment caused a redistribution of LDL-C subclasses towards less dense lipoprotein particles (possibly indicative of a less atherogenic LDL-C profile); however, the average LDL-C size did not change. Secondary: Omega-3 acid ethyl esters were well tolerated with no reports of drug-related adverse events or negative safety parameters (e.g., glucose, uric acid, liver enzymes, kidney function, and platelet count).
Calabresi et al.[38] (2004) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks vs placebo for 8 weeks	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 20 weeks	Primary: Changes in lipid profile, LDL-C and HDL-C subclass distribution	Primary: Plasma TG were 44% lower and LDL-C and apo B were 25% and 7% higher after omega-3 acid ethyl esters than placebo (all P<0.05). HDL-C was higher (8%) after omega-3 acid ethyl esters than placebo but this difference did not reach statistical significance (P>0.05). Omega-3 acid ethyl esters caused a selective increase of the more buoyant HDL2-C subfraction; plasma HDL2-C and total mass increased by 40% (P<0.05) and 26%, respectively, whereas HDL3-C and total mass decreased by 4% (P>0.05) and 6%. The plasma concentration of the HDL-bound antioxidant enzyme paraoxonase increased by 10% after omega-3 acid ethyl esters (P<0.05).
Roth et al.[18] (2009) <u>Phase I</u> Omega-3 acid ethyl esters 4 g (P-OM3) and fenofibrate 130 mg (FENO) once daily for 8 weeks	RCT, DB, PC, MC Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300 mg/dl,	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After 8 weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (P=0.059). There was no significant difference between the treatment groups (P=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to FENO monotherapy (+48.2% vs +39.0%, respectively; P=0.030).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fenofibrate 130 mg (FENO) once daily and placebo for 8 weeks <u>Phase II</u> Omega-3 acid ethyl esters 4 g (P-OM3) and fenofibrate 130 mg (FENO) once daily for 8 weeks				There was no significant difference in non-HDL-C among the treatment groups (-8.2% for P-OM3 + FENO vs -7.1% for FENO; P=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6% vs -47.6%, respectively; P=0.016). There was a greater reduction in remnant like particle cholesterol (RLP-C) with P-OM3 + FENO than with FENO monotherapy (-72.0% vs -62.1%; P=0.029). In the first 8-week extension study, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the double-blind treatment period (-17.5%, P=0.003). In the first 8-week extension study, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; P=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-15.4%, P=0.030 and -25.8%, P=0.035, respectively). There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the open-label phase of the study. In the pooled analysis of all patients enrolled in the 8-week open-label extension phase, the overall reductions of TGs and VLDL-C were -60.0% and -56.5%, respectively (both P<0.001). Non-HDLC and TC were also significantly reduced (P<0.001) over the 16-week treatment period in the pooled analysis. LDL-C increased +52.2% (P<0.001). There was no significant change in apolipoprotein B at the end of the 16-week treatment study (P=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events (AEs) were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis, dyspepsia, and headache.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stalenhoef et al.[40] (2000) Omega-3 acid ethyl esters (Omacor*) 4 g per day vs gemfibrozil 1,200 mg per day	DB, DD, RCT Patients with primary hypertriglyceridemia	N=28 12 weeks	Primary: Change in lipid profile, LDL-C subfraction profile	Primary: Both omega-3 acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C (P=0.05 to P<0.001 from baseline and P=0.29 to P=1.00 between groups). Both therapies resulted in a more buoyant LDL-C subfraction profile (P=0.05 for omega-3 acid ethyl esters, P<0.01 for gemfibrozil and P=0.09 between groups in favor of gemfibrozil).
van Dam et al.[41] (2001) Omega-3 acid ethyl esters (Omacor*) 4 g per day vs gemfibrozil 1,200 mg per day	RCT, DB Patients with hypertriglyceridemia (TG >400 mg/dl)	N=89 12 weeks	Primary: Percent change in TG Secondary: Percent change in TC, HDL-C, VLDL-C	Primary: The mean percent change in TG was −28.9% with omega-3 acid ethyl esters and –51.2% with gemfibrozil (P=0.007). Secondary: The mean percent change in HDL-C and TC were +1.2% and –10.2%, respectively, with omega-3 acid ethyl esters and +27.9% and –13.0%, respectively, with gemfibrozil (P=0.012 and P=0.513, respectively). The mean percent change in VLDL-C was -11.8% with omega-3 acid ethyl esters and -19.4% with gemfibrozil (P=0.494).
Bays et al.[50] (2010) Omega-3 acid ethyl ester (Lovaza®) 4 g per day for 16 weeks and atorvastatin 10 mg/day for 8 weeks, 20 mg for 4 weeks, and 40 mg for 4 weeks	RCT, DB, PC, MC Patients 18 to 79 years of age with hypercholesterolemia (non-HDL-C >160 mg/dl and TG 250 to 599 mg/dl)	N=245 16 weeks	Primary: Percent change in non-HDL-C level between baseline and week 8 Secondary: Percent changes in non-HDL-C level between baseline and the end of treatment with atorvastatin at	Primary: After 8 weeks of therapy, the median percent change in non-HDL-C was -40.2% in the omega-3 acid ethyl ester + atorvastatin group and -33.7% in the placebo + atorvastatin group (90% CI, -7.2% to -2.9%; P<0.001). Secondary: Omega-3 acid ethyl ester significantly reduced non-HDL-C compared to placebo during the atorvastatin 20 mg phase (-7.9%; 90% CI, -9.1% to -4.9%; P<0.001) and atorvastatin 40 mg phase (-4.1%, 90% Cl, -6.8% to -2.4%; P<0.001). There was no significant difference in the percentage of patients who achieved LDL-C goals with omega-3 acid ethyl ester + atorvastatin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 16 weeks and atorvastatin 10 mg/day for 8 weeks, 20 mg for 4 weeks, and 40 mg for 4 weeks			20 mg and 40 mg, percent changes in TC, HDL-C, LDL-C, VLDL-C, TG, apo A-I and apo B concentrations	(85.7%) or placebo + atorvastatin group (91.5%; P=0.20). There was no significant difference in the percentage of patients who achieved non-HDL-C goals with omega-3 acid ethyl ester + atorvastatin (88.7%) or placebo + atorvastatin group (87.8%; P>0.99). Treatment with omega-3-acid ethyl esters + atorvastatin (all doses) significantly reduced TC (P<0.001), TC:HDL-C ratio (P<0.001), TG (P<0.001), VLDL-C (P<0.001), remnant-like particle cholesterol (P<0.001) and increased HDL-C (P<0.001) compared to treatment with placebo + atorvastatin (all doses). There was no significant difference in LDL-C, apo A-I, or apo B between the treatment groups. There was no significant difference in adverse events among the treatment groups.
Durrington et al.[42] (2001) <u>Phase I</u> Omega-3 acid ethyl esters (Omacor*) 2 g BID and simvastatin for 24 weeks vs placebo and simvastatin once daily for 24 weeks <u>Phase II</u> Omega-3 acid ethyl esters (Omacor*) 2 g BID and simvastatin 10 to	RCT, DB Patients ≤75 years of age with established CHD who were already receiving treatment with simvastatin 10 to 40 mg daily and who had TG >203 mg/dl	N=59 48 weeks	Primary: Percent change in TG and VLDL-C, as well as effects on other lipid parameters	Primary: Serum triglyceride and VLDL-C significantly decreased with omega-3 acid ethyl esters compared to baseline or placebo (20-30% reduction, P<0.0005 and 30-40% reduction, P<0.005, respectively). There were no adverse effects on other lipid parameters with omega-3 acid ethyl esters, including LDL-C and HDL-C. There were no significant adverse events with omega-3 acid ethyl esters.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 mg QD for 24 weeks				
Nordoy et al.[43] (1998) Omega-3 acid ethyl esters (Omacor*) 4 g per day and simvastatin 20 mg once daily vs placebo and simvastatin 20 mg once daily	RCT, DB, PC Patients 25 to 60 years of age with combined hyperlipidemia receiving simvastatin 20 mg for 5-10 weeks	N=41 5 weeks	Primary: Lipid and lipoprotein parameters	Primary: The addition of omega-3 acid ethyl esters to simvastatin therapy led to an increase in EPA (P<0.0002) and DHA (P<0.0003) and reduction in linoleic acid (P=0.001). The addition of omega-3 acid ethyl esters to simvastatin led to a reduction in TC (P=0.052) and TG (P<0.001). There was no significant effect on HDL-C with omega-3 acid ethyl esters. There was no effect on apo A1 or apo B with the addition of omega-3 acid ethyl esters to simvastatin; however, there was a significant reduction in the concentration of apo E (P=0.035).
Davidson et al.[39] (2007) COMBOS Omega-3 acid ethyl ester (Lovaza®) 4 g/day and simvastatin 40 mg/day vs placebo and simvastatin 40 mg/day	DB, MC, PC, PG, RCT Patients 18 to 79 years of age who had received simvastatin 40 mg per day for at least 8 weeks, TG 200 to 500 mg/dL and LDL-C ≤10% above NCEP ATP III goal	N=254 16 weeks	Primary: Change in non-HDL-C Secondary: Changes in TG, VLDL-C, LDL-C, HDL-C, TC, and apo B; adverse events	Primary: At the end of treatment, the median percent change in non–HDL-C was significantly greater in the omega-3 acid ethyl ester plus simvastatin group than placebo plus simvastatin group (–9.0% vs –2.2%; P<0.001). Secondary: Treatment with omega-3 acid ethyl esters plus simvastatin was associated with significant reductions in TG (2.9% vs 6.3%) and VLDL-C (27.5% vs 7.2%), a significant increase in HDL-C (3.4% vs –1.2%) and a significant reduction in TC:HDL-C ratio (9.6% vs 0.7%; P<0.001). Adverse events reported by ≥1% of patients in the omega-3 acid ethyl esters group that occurred with a higher frequency than in simvastatin monotherapy group were nasopharyngitis (3.3%), upper respiratory tract infection (3.3%), diarrhea (2.5%) and dyspepsia (2.5%). There was no significant difference in the frequency of adverse events between groups.
Bays et al.[17] (2010) COMBOS	OL, ES Patients 18 to 79 years of age who had	N=188 24 months	Primary: Median percent change in non-HDL-C from	Primary: After 4 months of treatment in the extension study, the median percent change in non-HDL-C was –9.4% in Switchers and 0.9% in Non-switchers (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Omega-3 acid ethyl ester (Lovaza®) 4 g/day and simvastatin 40 mg/day	received simvastatin 40 mg per day for at least 8 weeks, TG 200 to 500 mg/dL and LDL-C ≤10% above NCEP ATP III goal		COMBOS end of treatment to month 4 of open-label treatment in the extension study Secondary: Median percent change in non-HDL-C at month 4, 12, and 24 in the extension phase; percent changes in TC, HDL-C, LDL-C, VLDL-C, TG	Secondary: After 4, 12, and 24 months of treatment in the extension study, the median percent change in non-HDL-C in the total population (Switchers and Non-switchers) was –8.3%, –7.3%, and –8.9%, respectively (all. P<0.001). After 4, 12, and 24 months of treatment in the extension study, TG and other lipoprotein lipid parameters revealed greater reductions in Switchers vs Non-switchers. After 4, 12, and 24 months of treatment in the extension study, the median percent reductions in TG, TC, and VLDL-C in the total population (Switchers and Non-switchers) were maintained (all, P<0.001). Treatment with omega-3 acid ethyl esters led to an increase in LDL-C from baseline at months 4, 12, and 24 in the total population (1.7%, P=NS; 6.2%, P<0.001; and 3.0%, P<0.05, respectively). Treatment with omega-3 acid ethyl esters led to a decrease in HDL-C from baseline at months 12 and 24 in the total population (-0.9%, P<0.05 and 3.0%, P<0.001, respectively). A total of 15.4% of patients experienced a serious adverse event (SAE). No deaths occurred during the study period. The most frequently reported treatment-emergent AEs were hypertension and bronchitis. The median absolute change in A1C after 24 months of treatment was 0.1%.
Maki et al.[48] (2008) Omega-3 acid ethyl esters (Lovaza®) 4 g/day and simvastatin 20 mg/day for 6 weeks vs	RCT, XO Patients 18 to 79 years of age with mixed dyslipidemia (TG 200 to 600 mg/dl and non-HDL-C above NCEP ATP III goal)	N=40 12 weeks	Primary: Lipid and lipoprotein parameters	Primary: Treatment with omega-3 acid ethyl esters + simvastatin resulted in a -40% reduction in non-HDL-C compared to -34% with placebo + simvastatin (P<0.001). Treatment with omega-3 acid ethyl esters + simvastatin also resulted in significantly greater changes in other lipid parameters compared to placebo + simvastatin, including VLDL-C (-42% vs -22%, respectively), TG (-44% vs -29%, respectively), TC (-31% vs -26%, respectively), and HDL-C (-16% vs -11%, respectively; P<0.05 for all). There was no significant difference in LDL-C with omega-3 acid ethyl esters +

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo and simvastatin 20 mg/day for 6 weeks				simvastatin (-37%) and placebo + simvastatin (-38%, P=0.433). Treatment with omega-3 acid ethyl esters + simvastatin resulted in significantly greater changes in other lipoprotein parameters compared to placebo + simvastatin, including apo B (-32% vs -28%, respectively), TC:HDL-C ratio (-39% vs -33%, respectively), and TG:HDL-C ratio (-51% vs -37%, respectively). There was no significant difference in ApoA-I levels with omega-3 acid ethyl esters + simvastatin (0.9) and placebo + simvastatin (4.3%, P=0.667).
Trials Assessing Cardiovascular Outcomes				
CDP Research Group[19] (1975) Niacin IR 3 g per day vs clofibrate 1.8 g per day vs placebo	DB, MC, PC, RCT Men aged 30-64 years with previous MI	N=8,341 5 years	Primary: Total mortality Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death), nonfatal cardiovascular events	Primary: The incidence of total mortality was comparable between niacin (24.4%), clofibrate (25.5%) and placebo (25.4%; all P=NS). Secondary: Five-year rates of death due to cardiovascular disease were comparable between niacin (18.8%), clofibrate (17.3%) and placebo (18.9%; all P=NS). Major cardiovascular events were reduced with niacin: CHD events by 13%, nonfatal MI by 27% and cerebrovascular events by 21%. Niacin treatment significantly reduced the incidence of nonfatal MI compared to placebo (8.9% vs 12.2%; P<0.004). There was no evidence of significant efficacy of clofibrate with regard to total mortality and cause-specific mortality. Treatment with niacin for 5 years lowered TC by 10% and TG levels by 26%. Treatment with clofibrate lowered TC by 7% and TG levels by 22%.
CDP Research Group[20] (1986) Niacin IR 3 g per day vs	DB, MC, PC, RCT Men aged 30-64 years with previous MI	N=8,341 9 years	Primary: Total mortality Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death)	Primary: A follow-up of patients 9 years after completion of the CDP study (total mean follow-up of 15 years) showed that niacin reduced the risk of all-cause mortality by 11% (52.0% for niacin and 58.2% for placebo; P=0.0004). Secondary: The survival benefit in the niacin group was primarily evident for death

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				caused by CHD (36.5% for niacin vs 41.3% for placebo; P<0.05).
Lee et al.[49] (2009) Niacin ER (Niaspan®) 2 g per day vs placebo	RCT, DB, PC, SC Patients with pre-existing atherosclerosis and low HDL-C (<40 mg/dl) in whom LDL-C was treated with statins	N=71 1 year	Primary: Absolute change in carotid artery wall area and change in carotid plaque index	Primary: Patients receiving niacin had a significantly greater change in carotid wall area at 12 months compared to placebo (difference -1.64 mm^2; 95% CI, -3.12 to -0.16; P=0.03). After 12 months of therapy, the change in carotid plaque index was significantly reduced by niacin compared to placebo (difference -0.016; 95% CI, -0.03 to -0.0022; P=0.02). Niacin increased HDL-C by 23% and decreased LDL-C by 19%. TG, apo B, and Lp(a) were significantly decreased by niacin compared to placebo. CRP was decreased by niacin compared with placebo (P=0.03 at 6 months and P=0.1 at 12 months). Adiponectin was significantly increased at both 6 and at 12 months (P<0.01).
Taylor et al.[23] (2004) Niacin ER (Niaspan®) 1 g per day vs placebo All patients received background statin therapy (specific statin not described).	DB, PC, RCT Patients with known coronary heart disease and low levels of HDL-C (<45 mg/dL)	N=167 1 year	Primary: Change in mean common CIMT after 1 year Secondary: Changes in lipid concentrations, composite of clinical cardiovascular events (including any hospitalization for an acute coronary syndrome, stroke, revascularization procedure or	Primary: After 12 months, mean CIMT increased significantly in the placebo group (0.044 mm; P<0.001) and was unchanged in the niacin group (0.014 mm; P=0.23). The overall difference in CIMT progression between the groups was not statistically significant (P=0.08); however, a post hoc analysis showed that niacin significantly reduced the rate of CIMT progression in patients without insulin resistance (P=0.026). Secondary: HDL-C increased 21% in the niacin group but did not change in the placebo group (P<0.003). Clinical cardiovascular events occurred in 3 patients treated with niacin (3.8%) and 7 patients treated with placebo (9.6%; P=0.20). Adherence to study medication based on pill counts ranged from 90.3% to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			sudden cardiac death), adverse events	94.5% and was not statistically different between the placebo and niacin groups. No patient experienced significant (3 times the ULN) elevations of liver enzymes or developed myositis. At the end of the study, skin flushing was reported to have occurred in 69.2% of patients receiving niacin compared to 12.7% of patients receiving placebo (P<0.001).
Taylor et al.[51] (2009) Niacin ER (Niaspan®) 2 g (titrated) once daily vs ezetimibe 10 mg once daily	RCT, OL, PG Patients ≥30 years of age with atherosclerotic coronary or vascular disease or a coronary heart disease risk equivalent (diabetes mellitus, 10-year Framingham risk score ≥20%, coronary calcium score >200 for women or >400 for men who were receiving treatment with a statin (LDL-C <100 mg/dl and HDL-C <50 mg/dl for men or <55 mg/dl for women)	N=208 14 months	Primary: Change in carotid intima-media thickness (IMT) after 14 months Secondary: Change in lipid values, composite of major adverse cardiovascular events (myocardial infarction, myocardial revascularization, admission to the hospital for an acute coronary syndrome, and death from coronary heart disease), discontinuation of study drug due to adverse effects, and health-related quality of life	Primary: Treatment with niacin led to a significant reduction in mean and maximal carotid intima–media thickness at 8 months (P=0.001 and P=0.004, respectively) and 14 months (P=0.001 and P<0.001, respectively). There was no significant change in mean or maximal carotid intima–media thickness with ezetimibe at 8 or 14 months compared to baseline. There was a significant difference between the niacin group and the ezetimibe group (P=0.003). Secondary: The change in LDL-C in the ezetimibe group was −17.6 mg/dl compared to -10.0 mg/dl in the niacin group (P=0.01). The change in HDL-C in the ezetimibe group was −2.8 mg/dl compared to 7.5 mg/dl in the niacin group (P<0.001). There were significant reductions in TGs in both groups. Major adverse cardiovascular events occurred in 5% of patients receiving ezetimibe compared to 1% of patients receiving niacin (P=0.04). Adverse drug effects led to withdrawal from the study in 3 of 9 patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12). There was no significant difference between the two groups in the quality of life at baseline or at 14 months.
Brown etal.[21] (2001)	DB, PC Patients with clinical	N=160 3 years	Primary: Changes in lipid profile,	Primary: The mean levels of LDL-C, HDL-C and TG were significantly changed by –42% (P<0.001), +26% (P<0.001) and –36% (P<0.001), respectively, in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HATS Niacin SR (Slo-Niacin®) titrated to 1 g twice daily and simvastatin vs antioxidants vs niacin SR (Slo-Niacin®) titrated to 1 g twice daily, simvastatin, and antioxidants vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.	coronary disease (defined as previous MI, coronary interventions or confirmed angina) and with at least 3 stenoses of at least 30% of the luminal diameter or 1 stenosis of at least 50%, low HDL-C, normal LDL-C		arteriographic evidence of change in coronary stenosis (% stenosis caused by most severe lesion in each of 9 proximal coronary segments), occurrence of first cardiovascular event (death from coronary causes, MI, stroke or revascularization) Secondary: Mean change in % stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions	the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups. Similar changes were observed when antioxidants were added to niacin plus simvastatin. The protective increase in HDL2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (+65%) was attenuated by concurrent therapy with antioxidants (+28%; P=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (P=0.16 compared to placebo) and 0.7% with niacin plus simvastatin plus antioxidants (P=0.004) and regressed by 0.4% with niacin plus simvastatin (P<0.001). The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower in the niacin plus simvastatin group than placebo (P=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group. Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.
GISSI-Prevenzione Investigators[34]	MC, OL, RCT Patients surviving a	N=11,324 3.5 years	Primary: Cumulative rate of all-cause death,	Primary: Treatment with omega-3 PUFA, but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI and nonfatal stroke (RR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1999) Omega-3 acid ethyl esters 1 g daily vs vitamin E 300 mg daily vs omega-3 acid ethyl esters 1 g daily and vitamin E 300 mg daily vs no treatment	recent (≤3 months) MI		nonfatal MI and nonfatal stroke; cumulative rate of CV death, nonfatal MI and nonfatal stroke Secondary: Analyses of components of primary end points and main causes of death, adverse events	10%; 95% CI, 1% to 18%; P=0.048 by 2-way analysis and RR, 15%; 95% CI, 2% to 26%; P=0.023 by 4-way analysis). Treatment with omega-3 PUFA decreased the risk of the composite of CV death, nonfatal MI and nonfatal stroke (RR 11%; 95% CI, 1% to 20%; P=0.053 by 2-way analysis and RR, 20%; 95% CI, 5% to 32%; P=0.008 by 4-way analysis). The effect of the combined treatment with omega-3 PUFA and vitamin E was similar to that for omega-3 PUFA for the primary end point (RR, 14%; 95% CI, 1% to 26%) and for fatal events (RR, 20%; 95% CI, 5% to 33%). Secondary: Analyses of the individual components of the main end point showed that the decrease in mortality (20% for total deaths, 30% for cardiovascular deaths [P=0.0242], and 45% for sudden deaths [P=0.010]) which was obtained with omega-3 PUFA accounted for all of the benefit seen in the combined end point. There was no difference across the treatment groups for nonfatal cardiovascular events. At 1 year and at the end of the study, 11.6% and 28.5% of patients receiving omega-3 PUFA and 7.3% and 26.2% of those receiving vitamin E, respectively, had permanently stopped taking the study drug. Side effects were reported as a reason for discontinuing therapy for 3.8% of patients in the omega-3 PUFA groups and 2.1% of those in the vitamin E groups. Overall, gastrointestinal disturbances and nausea were the most frequently reported side effects (4.9% and 1.4% of omega-3 PUFA recipients and 2.9% and 0.4% of vitamin E recipients, respectively).
Eritsland et al.[45] (1996) Omega-3 acid ethyl esters (Omacor®*) 4 g per day	RCT Patients admitted for coronary artery bypass grafting without concomitant cardiac surgery	N=610 1 year	Primary: Graft occlusion	Primary: After 1 year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving omega-3 acid ethyl esters compared to 33% in the control group (OR, 0.77, 95% CI, 0.60 to 0.99, P=0.034). In the omega-3 acid ethyl esters group, 43% of the patients had 21 vein grafts occluded compared with 51% of the patients in the control group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dietary therapy				(OR, 0.72, 95% CI, 0.51 to 1.01, P=0.05).
Johansen et al.[46] (1999) Omega-3 acid ethyl esters (Omacor*) 3 g twice dialy vs placebo	RCT, DB, PC Patients who were scheduled for elective coronary angioplasty for one or more lesions in native coronary arteries who had not undergone prior angioplasty	N=500 6 months	Primary: Restenosis	Primary: Restenosis occurred in 40.6% of the treated stenoses in the omega-3 acid ethyl esters group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; P=0.21). One or more restenoses occurred in 45.9% of patients treated with omega-3 acid ethyl esters compared to 44.8% of patients receiving placebo (OR, 1.05; 95% CI 0.69 to 1.59; P=0.82).
Nilsen et al.[44] (2001) Omega-3 acid ethyl esters (Omacor*) 3 g twice dialy vs placebo	RCT, SC, PC Patients >18 years of age with acute myocardial infarction	N=300 Up to 2 years	Primary: Cardiac events and revascularizations	Primary: Of the patients receiving omega-3 acid ethyl esters, 28% experienced at least one cardiac event compared to 24% of patients in the placebo group (P=0.74). There was no significant difference between the groups with regards to the number, type, or severity of cardiac events. There was no significant difference in the number of revascularizations with omega-3 acid ethyl esters or placebo (HR, 0.92; 95% CI 0.61 to 1.38).

*Omacor was renamed to Lovaza in August 2007.
Drug regimen abbreviations: BID=twice daily, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, HS=bedtime, IR=immediate release, IU=international units, PUFA=polyunsaturated fatty acids, QD=once daily, SR=sustained release, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, ES=extension study, MC=multicenter, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, XO=crossover
Miscellaneous abbreviations: A1C=hemoglobin A1c, ADMIT=Arterial Disease Multiple Intervention Trial, ADVENT=Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial, ALT=alanine aminotransferase, apo AI=apolipoprotein AI, apo B=apolipoprotein B, apo E=apolipoprotein E, ARBITER=ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol, AST=aspartate aminotransferase, CDP=Coronary Drug Project, CHD=coronary heart disease, CIMT=carotid intima-media thickness, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, FBG=fasting blood glucose, GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, HATS=HDL-Atherosclerosis Treatment Study, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, TC=total cholesterol, TG=triglycerides, ULN=upper limit of normal, VLDL-C=very low-density lipoprotein, VLDL-TG=very low-density lipoprotein triglycerides

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Antilipemic Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Niacin	extended-release tablet, sustained-release capsule*‡, sustained-release tablet*‡, tablet*‡	Niacor®, Niaspan®	$-$$$$	$
Omega-3 acid ethyl esters	capsule	Lovaza®	$$$$	N/A

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

X. Conclusions

Prescription niacin and omega-3 acid ethyl esters are approved by the FDA for the treatment of hypertriglyceridemia.[1-6] Prescription niacin is also approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia. Niacin is available over-the-counter in immediate-release and sustained-release formulations, which are currently on the Alabama Medicaid Preferred Drug List (PDL). Niacin is also available by prescription as immediate-release (Niacor®) and extended-release (Niaspan®) formulations. Omega-3 acid ethyl esters (Lovaza®) is only available by prescription. There are no generic formulations currently available for prescription niacin or omega-3 acid ethyl esters.

Guidelines for the treatment of lipid disorders identify LDL-C as the primary target of cholesterol lowering therapy. The HMG-CoA reductase inhibitors (statins) are generally considered first-line therapy in addition to therapeutic lifestyle changes (TLC).[11-16] For patients who cannot achieve LDL-C goals with the use of a statin alone, the addition of another LDL-C lowering drug such as niacin, a bile acid sequestrant or ezetimibe is recommended. In high-risk patients with high triglycerides or low HDL-C, consideration can be given to combination therapy with fibrates or niacin and an LDL-lowering agent.[11-15] If triglycerides are very high (≥500 mg/dl), triglyceride-lowering drugs (fibrate or nicotinic acid) become first-line therapy. When used at higher doses, omega-3 fatty acids lower triglycerides and are considered an alternative to fibrates or niacin for the treatment of hypertriglyceridemia.[12-13] Clinical trials suggest that relatively high intakes of omega-3 fatty acids in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD.[12]

Niacin is the most effective agent for modifying all of the lipid abnormalities associated with atherogenic dyslipidemia, and it is the most effective agent for raising HDL-C.[12] Clinical trials have demonstrated that niacin positively impacts a variety of lipid/lipoprotein parameters.[24-33,47,52-53] Niacin has been shown to reduce the risk of recurrent nonfatal myocardial infarction in patients with hypercholesterolemia, as well as slow the progression or promote regression of atherosclerotic disease (in combination with bile acid sequestrants) in patients with a history of coronary artery disease and hypercholesterolemia.[4-5,19-21] There are limited head-to-head studies comparing the efficacy and safety of the different niacin formulations.[30-32] While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release and extended-release products. Cases of severe hepatic toxicity have occurred in patients who have substituted sustained-release niacin products for immediate-release niacin at equivalent doses.[4-5] Due to significant safety concerns, the AHA stresses that dietary supplement niacin must not be used as a substitute for prescription niacin, and should not be used for cholesterol lowering due to the potential for very serious side effects.[10]

Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.[17-18,35-39,42-43,48,50] The effect of prescription omega-3 acid ethyl esters (Lovaza®) on cardiovascular mortality and morbidity in patients with elevated triglycerides has not been determined.[6]

Therefore, prescription niacin products (Niacor® and Niaspan®) offer significant clinical advantages in general use over the other brands, generics and OTC niacin products in the same class (if applicable), but are comparable to each other. Due to its limited FDA-approved indications, prescription omega-3 acid ethyl esters should be available through the medical justification portion of the prior authorization process for adults with severe hypertriglyceridemia (≥500 mg/dl).

XI. Recommendations

Prescription niacin is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand prescription niacin product is selected as a preferred agent.

No brand omega-3 acid ethyl ester 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 Nitrates and Nitrites
AHFS Class 241208
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I. Overview

Angina occurs when myocardial oxygen demand exceeds supply, which results in chest discomfort or pain. Common treatments for chronic angina include nitrates, β-blockers and calcium channel blockers.[51] The nitrites and nitrates reduce oxygen demand by decreasing left ventricular pressure and systemic vascular resistance, as well as by dilating coronary arteries.[1-14] β-blockers reduce heart rate and contractility by competitively blocking the response to beta-adrenergic stimulation in the heart. Calcium channel blockers increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction and reducing contractility. They also decrease oxygen demand by reducing systemic vascular resistance and arterial pressure.

Tolerance develops after chronic exposure to nitrates, regardless of the route of administration or formulation used.[1-14] This can be overcome by instituting short periods (10-12 hours) of withdrawal from nitrate therapy.[1-14] For example: administer the last dose of a short-acting product prior to 7:00 p.m., administer products twice daily instead of four times daily, or use sustained-release products once daily in the morning.[1-3]

In March 2010, the FDA sent warning letters to two companies (Glenmark Generics, Inc. and Konec, Inc.) ordering them to cease marketing unapproved generic sublingual nitroglycerin tablets (0.3 mg, 0.4 mg, and 0.6 mg).[50] According to information found on the FDA's website, these companies have 90 days from the date of the warning letters to cease manufacturing new products and 180 days to cease further shipment of existing products. Previously manufactured unapproved affected products may still be found on pharmacy shelves for a short period of time following these deadlines.

The nitrates and nitrites that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in May 2008.

Table 1. Nitrates and Nitrites Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amyl nitrite	inhalant	N/A	amyl nitrite
Isosorbide dinitrate	sublingual tablet, sustained-release capsule, sustained-release tablet, tablet	Dilatrate-SR®, Isordil®*, Isordil Titradose®*	isosorbide dinitrate
Isosorbide mononitrate	sustained-release tablet, tablet	Imdur®*, Ismo®*, Monoket®*	isosorbide mononitrate
Nitroglycerin	injection, ointment, sublingual tablet, transdermal patch, translingual spray	Minitran®*, Nitro-Bid®*, Nitro-Dur®*, Nitrolingual®, Nitrostat®*, Nitromist®†	nitroglycerin§, Nitro-Bid®*

*Generic is available in at least one dosage form or strength.
§Covered generic sublingual nitroglycerin tablets are not FDA-approved and will no longer be manufactured.[50]
†Product was added to Medicaid's drug file after the meeting's drug list was approved.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the nitrates and nitrites are summarized in Table 2.

Table 2. Treatment Guidelines Using the Nitrates and Nitrites

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement (ICSI): **Stable Coronary Artery Disease[28] (2009)**	• In patients with mild, stable coronary artery disease, drug therapy may be limited to short-acting sublingual nitrates on an as-needed basis. Use of lower dose (e.g., 0.3 mg or one-half of a 0.4 mg tablet) may reduce the incidence of side effects such as headache or hypotension in susceptible patients. • β-blockers should be used in all patients following a myocardial infarction based on studies showing mortality reduction. They are also the preferred first-line therapy for reducing symptoms of angina in patients with stable coronary artery disease. • If β-blockers cannot be prescribed as first-line therapy, nitrates are the preferred alternative first-line therapy because of efficacy and relatively few side effects. • Tolerance to long-acting nitrates is an important clinical issue in some patients and can be avoided by appropriate daily nitrate-free intervals. • For patients who are unable to take β-blockers or long-acting nitrates, the use of calcium channel blockers has been shown to be clinically effective in decreasing symptoms of angina. Calcium channel blockers have not been proven to reduce mortality. Because β-blockers have reduced mortality in the post-myocardial infarction period, they are the preferred agent for patients with stable coronary artery disease. • Combination therapy may be necessary in selected patients. A combination of β-blockers and long-acting nitrates is preferred because of efficacy and reduced potential for adverse side effects.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina[16] (2007)**	• Use sublingual nitroglycerin or nitroglycerin spray for immediate relief of angina. • ACE inhibitors should be started and continued indefinitely in all patients with LVEF ≤40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • It is reasonable to use ACE inhibitors among lower-risk patients with mildly reduced or normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed. • Angiotensin receptor blockers are recommended for patients who have hypertension, have indications for but are intolerant of ACE inhibitors, have heart failure, or have had a myocardial infarction with LVEF ≤40%. • Angiotensin receptor blockers may be considered in combination with ACE inhibitors for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended for use in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40%, and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Refer to the 2002 guidelines for additional information regarding the treatment of chronic stable angina.[52]
National Institute for Health and Clinical Excellence (NICE):	• In patients with a prior myocardial infarction without heart failure, CCBs, nitrates, and potassium channel activators have no effect on

Clinical Guideline	Recommendation(s)
Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction[24] (2007)	premature mortality. They can be used for management of risk factors such as hypertension in patients intolerant to a β-blocker and an ACE inhibitor.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris[21] (2006)**	• ACE inhibitor therapy is indicated in patients with hypertension, heart failure, left ventricular dysfunction with or without history of prior myocardial infarction, or diabetes. • β-blockers are indicated for most patients with more than mild angina, unless contraindicated. Long-acting nitrates or CCBs may be considered if β-blockers are contraindicated. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. • If CCBs alone or in combination with β-blockers do not adequately relieve symptoms, long-acting nitrates should be considered. • Long-acting nitrates have shown no clinical benefit over either β-blockers or CCBs. • Short-acting nitrates may be used for prompt relief or prevention of angina, and should be offered to all patients. • Continuous transdermal nitroglycerin therapy is ineffective and it is recommended that patches be removed for a portion of the day.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease[20] (2004)**	• β-blockers should be strongly considered as initial therapy, unless contraindicated. • ACEIs should be recommended for patients with symptomatic chronic stable angina to prevent myocardial infarction and death and to reduce symptoms of angina, and in patients with asymptomatic chronic stable angina with coronary artery disease, who also have diabetes mellitus, systolic dysfunction, or both. • Sublingual nitroglycerin or nitroglycerin spray should be given for immediate angina symptomatic relief. • Long-acting CCB or long-acting nitrates may be used with β-blockers if initial treatment is not successful or if β-blockers are contraindicated. • Nitrates have not demonstrated any reduction in mortality in either post-myocardial infarction (MI) patients or in patients with coronary artery disease (CAD).
American College of Cardiology (ACC)/American Heart Association (AHA): **2002 Guideline Update for the Management of Patients With Chronic Stable Angina[52] (2002)**	• Aspirin 75-325 mg should be used routinely in all patients with acute and chronic ischemic heart disease unless contraindicated. Clopidogrel may be used when aspirin is contraindicated. • β-blockers should be considered as initial therapy for chronic stable angina. • HMG-CoA reductase inhibitors should be recommended even in mild-to-moderate elevations of low-density lipoprotein cholesterol (LDL-C). • ACE inhibitors should be prescribed to patients with diabetes and/or left ventricular systolic dysfunction. • There is insufficient evidence for using an angiotensin receptor blocker in chronic stable angina. • Use sublingual nitroglycerin or nitroglycerin spray for immediate relief of angina. • Long-acting CCBs or long-acting nitrates may be used if β-blockers are contraindicated. • An immediate-release and short-acting dihydropyridine CCB can increase adverse cardiac events and should not be used. • A long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-segment Elevation (STEMI)[23] (2008)**	• Nitrates are recommended for use in mild heart failure (Killip Class II) and severe heart failure (Killip Class III) unless the patient is hypotensive when there is pump failure or cardiogenic shock. • Nitroglycerin may produce some improvement if there is no cardiogenic shock, but intra-aortic balloon counter pulsation is the most effective method of providing circulatory support while preparing for surgery.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (STEMI) [18] (2004)**	Initial Emergency Department Management • Sublingual nitroglycerin 0.4 mg should be given to patients with ongoing ischemic discomfort every 5 minutes for 3 total doses. After 3 doses, assess need for IV nitroglycerin. • IV nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension or management of pulmonary congestion. Hospital Management–Medication Assessment • IV nitroglycerin is indicated during the first 48 hours for treatment of persistent ischemia, hypertension or congestive heart failure (CHF), provided that therapy does not preclude treatment with β-blockers or ACE inhibitor. • NTG after 48 hours can be useful for recurrent angina or persistent CHF provided that therapy does not preclude treatment with β-blockers or ACE inhibitor. • In 2007 and 2009, an update to this guideline was published but it did not address the use of the nitrates or nitrites.[19,31]
American College of Cardiology (ACC)/American Heart Association (AHA): **Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[17] (2007)**	Clinical Assessment • Patients with suspected acute coronary syndrome should be instructed to take no more than 1 dose of sublingual nitroglycerin for chest pain or discomfort. If additional doses are required for persistent or worsening pain, emergency medical attention should be sought. Additional nitroglycerin may be taken every 5 minutes for a total of 3 doses while awaiting an ambulance. • Patients with chronic stable angina should be instructed that if symptoms are significantly improved after the first dose of sublingual nitroglycerin, doses can be repeated every 5 minutes if needed for a total of 3 doses. If pain does not completely resolve after 3 doses, immediate medical attention should be sought. • Instructions for sublingual nitroglycerin administration may be individualized for patients who are known to have frequent angina episodes. The frequency and characteristics of symptoms, as well as the typical response time should be evaluated to determine an appropriate plan. Immediate Management • Low-risk patients that are referred to outpatient stress testing should be given medications such as sublingual nitroglycerin, aspirin and/or β-blockers as a preventative measure. Anti-Ischemic Therapy • Sublingual nitroglycerin (0.4 mg) should be given to patients with UA/NSTEMI and continuing angina every 5 minutes as needed for up to 3 doses. An evaluation of the need for intravenous (IV) nitroglycerin, if not contraindicated, should then be performed. • An evaluation as to whether to administer IV nitroglycerin should be performed after alternative mortality-reducing interventions with agents such as β-blockers or ACE inhibitors have been utilized. • IV nitroglycerin is indicated during the first 48 hours after UA/NSTEMI and continuing ischemia, heart failure (HF) or hypertension.

Clinical Guideline	Recommendation(s)
	• The recommended starting dose of IV nitroglycerin is 10 mcg/min and then titrated by 10 mcg/min every 3-5 minutes until patient is either nonsymptomatic or a response in blood pressure is seen. • Once the dose has reached 20 mcg/min and no response has been noted, an increase of 10 mcg/min and then 20 mcg/min may be used. • In the absence of relief of symptoms, the goal is to achieve a response in blood pressure. Once this is reached, the dose of IV nitroglycerin should then be decreased and the dosing intervals should be extended. • The maximum dose of IV nitroglycerin has not been established although it is generally considered to be 200 mcg/min. • Topically or orally administered nitrates are considered options for patients without persistent refractory ischemic symptoms but who require additional treatment for angina. • Once patients have been symptom-free for 12-24 hours IV nitroglycerin doses should be decreased and converted to oral or topical nitrates. • Nitrates should not be given under the following circumstances: in patients with UA/NSTEMI with systolic blood pressure <90 mm HG or ≥30 mm Hg below baseline, in cases of severe bradycardia [<50 beats per minute (bpm)], in patients with tachycardia (>100 bpm) in nonsymptomatic heart failure or right ventricular infarction. • Nitrates are also contraindicated within 24 hours of receiving sildenafil or 48 hours of taking tadalafil. The appropriate time between vardenafil utilization and nitrate administration has not been established. • Nitrate-free intervals are recommended in patients on oral or topical nitrates and decreases in IV doses should be attempted whenever possible to avoid tolerance. <u>Post-UA/NSTEMI</u> • All patients post-UA/NSTEMI should be given sublingual or spray nitroglycerin. • Sublingual nitroglycerin should be used for anginal discomfort that has not been relieved by discontinuation of activity or removal from a stressful event. If symptoms persist or worsen after 5 minutes emergency medical services should be contacted. Doses can be repeated every 5 minutes if needed for 3 total doses while patient is lying down or sitting. <u>Long-Term Medical Therapy and Secondary Prevention</u> • NTG is recommended to treat ischemic symptoms.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE-ACS)**[22] **(2007)**	• Intravenous nitrates may be considered in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) who require hospitalization. Once symptoms are controlled, a non-parenteral alternative should be used at intermittent dosing intervals to avoid tolerance. • Nitrates administered IV or orally are effective in treating acute symptoms of angina. • Patients with NSTE-ACS should be initiated on sublingual or IV nitroglycerin with caution given to those with systolic blood pressure <90 mm Hg.
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS)**[33] **(2008)**	• Nitroglycerin should be given sublingually (0.4 mg every five minutes) to relieve ischemic symptoms. If symptoms are ongoing or recurrent despite the administration of intravenous access β-blockers, intravenous access nitroglycerin can be initiated at 10 mcg/min and titrated every 3 to 5 minutes by 10 mcg/min until symptom response is noted or blood pressure decreases to less than 110 mm Hg in patients

Clinical Guideline	Recommendation(s)
	previously normotensive or by 25% in patients who were hypertensive on presentation, or to a maximum dose of 200 mcg/min. Patients can be converted to topical or oral nitrates once stabilized (no manifestations of ischemia and pain free for 12 to 24 hours). • ISIS-4 and GISSI-3 failed to show a benefit of nitroglycerin on reduction of mortality in acute myocardial infarction. • Nitroglycerin is contraindicated in patients who are hypotensive, have documented severe aortic stenosis, have hypertrophic cardiomyopathy, or who have received sildenafil, vardenafil, or ordenafil within the previous 24 hours or tadalafil in the previous 48 hours. • Oral nitrates may benefit patients who have a non-ST-elevation myocardial infarction with postinfarction angina or congestive heart failure. • Upon hospital discharge for those who required percutaneous intervention, oral nitrates should be considered for patients with ongoing ischemia.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: Guidelines for the Diagnosis and Management of Chronic Heart Failure in Adults**[32] **(2009)**	• The combination of a fixed-dose hydralazine and isosorbide dinitrate is recommended to improve outcomes for African-American patients with moderate-severe symptoms (NYHA functional class III or IV heart failure) on optimal therapy with ACE inhibitors, β-blockers, and diuretics. • The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of heart failure in patients who have no prior use of an ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty. • The addition of a combination of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an ACE inhibitor and β-blocker for symptomatic heart failure, but who have persistent symptoms. • A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction (LVEF) who cannot be given an ACE inhibitor or an ARB because of drug intolerance, hypotension, or renal insufficiency. • Patients with heart failure should be given nitrates and β-blockers for the treatment of angina. • In patients with evidence of severely symptomatic fluid overload in the absence of systemic hypotension, vasodilators, such as nitroglycerin, can be beneficial when added to diuretics when diuretics alone are not effective. • Patients with heart failure and hypertension, coronary ischemia, or significant mitral regurgitation are often cited as ideal candidates for the use of intravenous nitroglycerin. • Refer to the 2005 guidelines for additional information regarding the treatment of chronic heart failure.[25]
Institute for Clinical Systems Improvement (ICSI): **Heart Failure in Adults**[15] **(2009)**	<u>Treatment of Systolic Dysfunction</u> • The cornerstone of treatment is the use of β-blockers and ACE inhibitors. • Patients who are intolerant of ACE inhibitors may benefit from the combination of hydralazine and nitrates. This treatment has been shown to improve survival compared to placebo, but is less effective than ACE inhibitors. ARB's are recommended for patients intolerant of ACE inhibitors. • The combination of hydralazine and nitrates is recommended in African Americans with moderate-to-severe symptoms on optimal

Clinical Guideline	Recommendation(s)
	therapy with ACE inhibitors, β-blockers and diuretics. • Digoxin improves symptoms for patients in sinus rhythm with ventricular dilatation, elevated filling pressures and a third heart sound. • Digoxin improves symptoms, exercise tolerance and quality of life but does not increase or decrease mortality. • Digoxin is beneficial in heart failure patients with reduced LVEF to decrease hospitalizations for heart failure. • Diuretics should be used to control fluid retention. • Aldosterone antagonists have been shown to reduce mortality. The addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of heart failure and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Treatment of Heart Failure with Preserved Ejection Fraction (HFPEF) • In general, drugs used to treat systolic dysfunction (ACE, ARBs, diuretics, β-blockers) are generally used in patients with heart failure with preserved systolic function but indicated to manage comorbidities Atrial Fibrillation in Heart Failure • β-blockers and digoxin used alone or in combination are the drugs of choice for achieving rate control. • Digoxin is effective in controlling ventricular rate at rest, but may not achieve satisfactory rate control with exertion. Acute Treatment of Heart Failure • Digoxin, as an inotrope, is not useful in the acute management of decompensated heart failure.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[27] **(2008)**	Management of Chronic Heart Failure: • In symptomatic patients with a left ventricular ejection fraction ≤40%, the combination of hydralazine and isosorbide dinitrate may be used as an alternative if there is intolerance to both an ACE inhibitor and angiotensin receptor blocker. • Adding the combination of hydralazine should be considered in patients with persistent symptoms despite treatment with an ACE inhibitor, β-blocker, and an angiotensin receptor blocker or aldosterone antagonist. • Treatment with hydralazine and isosorbide dinitrate in these patients may reduce the risk of death, reduces hospital admission for worsening heart failure, and improves ventricular function and exercise capacity. • The evidence supporting this combination is strongest in patients of African-American descent. • This combination is contraindicated in patients with symptomatic hypotension, Lupus syndrome, and severe renal failure. Management of Acute Heart Failure: • Intravenous nitroglycerin or isosorbide dinitrate are recommended at an early stage for acute heart failure patients without symptomatic hypotension, systolic blood pressure <90 mmHg or serious obstructive valvular disease. • In patients in acute heart failure with pulmonary edema, vasodilators are recommended when blood pressure is normal or high. • In patients in acute heart failure and hypertensive, vasodilators are recommended with close monitoring and low-dose diuretic treatment in patients with volume overload or pulmonary edema.
Heart Failure Society of America (HFSA): C**omprehensive Heart Failure Practice Guidelines**[26]	• Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE inhibitor for African Americans with left ventricular systolic dysfunction. • May be considered in non–African American patients with left

Clinical Guideline	Recommendation(s)
(2006)	ventricular dysfunction (LVD) who remain symptomatic despite optimized standard therapy and in patients who do not tolerate ARB therapy.
American College of Cardiology (ACC)/American Heart Association (AHA): **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult**[25] **(2005)**	• The addition of a combination of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an ACEI and β-blocker for symptomatic heart failure, but who have persistent symptoms. • A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction (LVEF) who cannot be given an ACEI or an angiotensin II receptor blocker (ARB) because of drug intolerance, hypotension, or renal insufficiency. • Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACEI for African Americans with New York Heart Association (NYHA) functional class III or IV heart failure. Any potential benefit in other patients has yet to be evaluated. • Patients with heart failure should be given nitrates and β-blockers for the treatment of angina.
National Institute for Health and Clinical Excellence (NICE): **Management of Chronic Heart Failure in Adults in Primary and Secondary Care**[29] **(2003)**	• An isosorbide/hydralazine combination may be used in patients with heart failure who are intolerant to ACE inhibitors or ARB's.
European Society of Cardiology (ESC): **Guidelines for Pre-Operative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery**[34] **(2009)**	• Nitroglycerin has been shown to reverse myocardial ischemia. • Perioperative nitroglycerin use for the prevention of adverse ischemic events may be considered
Joint National Committee (JNC): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure**[30] **(2003)**	• Intravenous nitroglycerin, at a rate of 5-100 mcg/min, is among the treatment options for the management of hypertensive emergencies, particularly in the setting of coronary ischemia. • Intravenous nitroglycerin's onset and duration of action are 2-5 minutes and 5-10 minutes, respectively.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the nitrates and nitrites 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 Nitrates and Nitrites[1-14]

Indication	Amyl Nitrite	Isosorbide Dinitrate†	Isosorbide Mononitrate†	Nitroglycerin		
				Tablet/ Spray	Injection	Topical/ Transdermal†
Angina Pectoris						
Acute relief of an attack of angina pectoris	✔			✔		
Prevention of angina pectoris due to coronary artery disease		✔	✔	✔		✔
Treatment of angina pectoris due to coronary artery disease		✔	✔			
Treatment of angina pectoris in patients who have not responded to sublingual nitroglycerin and β-blockers					✔	
Cardiovascular Uses						
Control of congestive heart failure in the setting of acute myocardial infarction					✔	
Induction of intraoperative hypotension					✔	
Treatment of perioperative hypertension					✔	

†The onset of action of oral isosorbide dinitrate, oral isosorbide mononitrate, oral nitroglycerin capsules, or transdermal nitroglycerin is not sufficiently rapid for these products to be useful in aborting an acute anginal episode.

IV. Pharmacokinetics

The pharmacokinetic parameters of the nitrates and nitrites are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Nitrates and Nitrites[1-14]

Generic Name(s)	Bioavailability (%)	Onset (minutes)	Duration	Excretion (%)	Half-Life
Amyl nitrite	Not reported	0.5	5-10 min	Not reported	Not reported
Isosorbide dinitrate	IR: 58 SL: 19-93 SR: 22	IR: 45-60 SL: 2-10 SR: 60	IR: 8 hours SL: 1-2 hours SR: 8 hours	Renal (80-90) Feces	IR: 4 hours SL: 1 hours SR: 4 hours
Isosorbide mononitrate	IR: 93-100 SR: 80-100	IR: 45-60 SR: 30-60	IR: 6 hours SR: 12 hours	Renal (78) Feces (1)	IR: 6 hours SR: 6 hours
Nitroglycerin	Oint: 75 Patch: 75 SL: 38.5	IV: 1-5 Oint: 30-60 Patch: 30-60 SL: 1-3	IV: 5-10 min Oint: 2-12 hours Patch: 18-24 hours SL: 30-60 min	Liver (extensive)	1-4 min

IR=immediate-release, Oint=ointment, SL=sublingual, SR=sustained-release

V. Drug Interactions

Significant drug interactions with the nitrates and nitrites are listed in Table 5.

Table 5. Significant Drug Interactions with the Nitrates and Nitrites[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Nitrates and nitrites	1	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Nitroglycerin	1	Alteplase	Concentrations of tissue-type plasminogen activator (tPA) are decreased, indicating impairment of the thrombolytic effect of alteplase. The enhanced hepatic blood flow as a result of the nitroglycerin facilitates the hepatic metabolism of tPA.
Nitrates and nitrites	2	Dihydroergotamine	The metabolism of dihydroergotamine is decreased thus increasing its bioavailability. The dose of the dihydroergotamine may need to 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 nitrates and nitrites are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Nitrates and Nitrites[1-14]

Adverse Events	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Cardiovascular					
Abnormal heart sound	-	-	≤5	-	-
Aggravated angina pectoris	-	-	≤5	-	-

Adverse Events	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Angina pectoris	-	-	-	≥1	-
Arrhythmia	-	-	≤5	<1	-
Atrial fibrillation	-	-	≤5	<1	-
Bradycardia	-	-	≤5	-	-
Bundle branch block	-	-	≤5	-	-
Cardiac failure	-	-	≤5	-	-
Crescendo angina	-	✔	-	-	✔
Extrasystole	-	-	≤5	-	-
Flushing	✔	-	≤5	-	✔
Heart murmur	-	-	≤5	-	-
Hypertension	-	-	≤5	-	-
Hypotension	✔	✔	≤5	<1	4
Migraine	-	-	≤5	-	-
Myocardial infarction	-	-	≤5	✔	-
Palpitation	✔	-	≤5	<1	✔
Postural hypotension	✔	✔	-	<1	✔
Premature ventricular contraction	-	-	-	<1	-
Q wave abnormality	-	-	≤5	-	-
Rebound hypertension	-	✔	-	-	✔
Supraventricular tachycardia	-	-	-	<1	-
Syncope	✔	✔	✔	<1	✔
Tachyarrhythmia	✔	-	-	-	-
Tachycardia	✔	-	≤5	-	-
Ventricular tachycardia	-	-	≤5	-	-
Central Nervous System					
Anxiety	-	-	≤5	<1	-
Confusion	-	-	≤5	<1	-
Decreased libido	-	-	≤5	-	-
Depression	-	-	≤5	-	-
Dizziness	✔	✔	8-11	3-5	≥2
Headache	✔	✔	≥5	19-38	50-63
Impotence	-	-	≤5	<1	-
Insomnia	-	-	≤5	<1	-
Lightheadedness	✔	✔	-	-	6
Nervousness	-	-	≤5	<1	-
Neuritis	-	-	≤5	-	-
Paresis	-	-	≤5	-	-
Paresthesia	-	-	≤5	-	≥2
Purpura	-	-	≤5	-	-
Somnolence	-	-	≤5	-	-
Vertigo	-	-	≤5	-	✔
Dermatological					
Acne	-	-	≤5	-	-
Anaphylactoid reactions	-	-	-	-	✔
Contact dermatitis	✔	-	-	-	✔ *
Exfoliative dermatitis	-	-	-	-	✔
Photophobia	-	-	≤5	-	-
Pruritus	-	-	≤5	<1	-
Rash	✔	-	≤5	<1	✔
Skin nodule	-	-	≤5	-	-
Gastrointestinal					
Abdominal pain	-	-	≤5	<1	≤2
Constipation	-	-	≤5	-	-

Adverse Events	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Diarrhea	-	-	≤5	<1	-
Dyspepsia	-	-	≤5	<1	-
Flatulence	-	-	≤5	-	-
Gastric ulcer	-	-	≤5	-	-
Gastritis	-	-	≤5	-	-
Hemorrhagic gastric ulcer	-	-	≤5	-	-
Loose stools	-	-	≤5	-	-
Nausea	✔	-	≤5	2-4	✔
Vomiting	✔	-	≤5	2-4	✔
Genitourinary					
Dysuria	-	-	-	<1	-
Polyuria	-	-	≤5	-	-
Renal calculus	-	-	≤5	-	-
Urinary tract infection	-	-	≤5	-	-
Hematologic					
Hemolytic anemia	✔	-	-	-	-
Hypochromic anemia	-	-	≤5	-	-
Methemoglobinemia	✔	✔	✔	✔	✔
Thrombocytopenia	-	-	≤5	-	-
Laboratory Test Abnormalities					
Elevated SGOT	-	-	≤5	-	-
Elevated SGPT	-	-	≤5	-	-
Musculoskeletal					
Arthralgia	-	-	≤5	<1	-
Asthenia	✔	-	≤5	<1	-
Muscle weakness	-	-	≤5	-	-
Musculoskeletal pain	-	-	≤5	-	-
Myalgia	-	-	≤5	-	-
Respiratory					
Bronchitis	-	-	≤5	<1	-
Bronchospasm	-	-	≤5	-	-
Coughing	-	-	≤5	-	-
Dyspnea	✔	-	≤5	-	≤2
Increased sputum	-	-	≤5	-	-
Nasal congestion	-	-	≤5	-	-
Pharyngitis	-	-	≤5	-	-
Pneumonia	-	-	≤5	<1	-
Pulmonary infiltration	-	-	≤5	-	-
Rales	-	-	≤5	-	-
Rhinitis	-	-	≤5	-	-
Sinusitis	-	-	≤5	-	-
Upper respiratory tract infection	-	-	-	<1	-
Other					
Abnormal hair texture	-	-	≤5	-	-
Abnormal vision	-	-	≤5	-	-
Agitation	-	-	-	<1	-
Atrophic vaginitis	-	-	≤5	-	-
Back pain	-	-	≤5	-	-
Bacterial infection	-	-	≤5	-	-
Blurred vision	-	✔	-	<1	-
Breast pain	-	-	≤5	-	-
Chest pain	-	-	≤5	-	-
Cold sweat	-	-	-	<1	-

Adverse Events	Amyl Nitrite	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Collapse	-	-	-	-	✔
Conjunctivitis	-	-	≤5	-	-
Diplopia	-	-	-	<1	-
Dry mouth	-	-	≤5	-	-
Discoordination	-	-	-	<1	-
Earache	-	-	≤5	-	-
Edema	-	-	≤5	<1	-
Fatigue	-	-	≤5	-	-
Fever	-	-	≤5	-	-
Flu-like symptoms	-	-	≤5	-	-
Frozen shoulder	-	-	≤5	-	-
Glossitis	-	-	≤5	-	-
Hemorrhoids	-	-	≤5	-	-
Hot flashes	-	-	≤5	-	-
Hyperuricemia	-	-	≤5	-	-
Hypoesthesia	-	-	≤5	<1	-
Hypokalemia	-	-	≤5	-	-
Hypokinesia	-	-	-	<1	-
Impaired concentration	-	-	≤5	-	-
Increased appetite	-	-	-	<1	-
Increased sweating	-	-	≤5	-	-
Intermittent claudication	-	-	≤5	-	-
Leg ulcer	-	-	≤5	-	-
Malaise	-	-	≤5	<1	-
Melena	-	-	≤5	-	-
Moniliasis	-	-	≤5	-	-
Myositis	-	-	≤5	-	-
Nightmares	-	-	-	<1	-
Pallor	-	-	-	-	✔
Paroniria	-	-	≤5	-	-
Ptosis	-	-	≤5	-	-
Restlessness	✔	-	-	-	✔
Rigors	-	-	≤5	<1	-
Tendon disorder	-	-	≤5	-	-
Tenesmus	-	-	-	<1	-
Tinnitus	-	-	≤5	-	-
Tooth disorder	-	-	-	<1	-
Tremor	-	-	≤5	-	-
Tympanic membrane perforation	-	-	≤5	-	-
Varicose veins	-	-	≤5	-	-
Viral infection	-	-	≤5	-	-
Weakness	-	-	-	-	✔

IR=immediate-release, SR=sustained-release
*Topical formulation only.
✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the nitrates and nitrites are listed in Table 7.

Table 7. Usual Dosing Regimens for the Nitrates and Nitrites[1-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amyl nitrite	Angina: Inhalant: 1-6 inhalations from 1 crushed ampul, repeat in 3-5 minutes as needed	Safety and efficacy in children have not been established.	Inhalant
Isosorbide dinitrate	Angina: Tablet (sublingual): 2.5-5 mg every 5-10 minutes for maximum of 3 doses in 15-30 minutes; may also use prophylactically 15 minutes prior to activities which may provoke an attack Capsule/tablet (SR): 40 mg every 8-12 hours; maximum: 160 mg daily Tablet: initial, 5-40 mg four times/day	Safety and efficacy in children have not been established.	Capsule (SR): 40 mg Tablet: 5 mg 10 mg 20 mg 30 mg 40 mg Tablet (SR): 40 mg Tablet (sublingual): 2.5 mg 5 mg
Isosorbide mononitrate	Angina: Tablet (SR): initial, 30-60 mg once daily; dose can be titrated as needed with at least 3 days between increases; maximum daily single dose, 240 mg Tablet: 5-20 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg Tablet (SR): 30 mg 60 mg 120 mg
Nitroglycerin	Angina: Injection: 5 mcg/min; increase 5 mcg/min every 3-5 minutes up to 20 mcg/min. If no response at 20 mcg/min, increase by 10 mcg/min every 3-5 minutes, up to 200 mcg/min Ointment: initial, 1/2 to 2 inch twice daily with the second dose applied 6 hours later Tablet (sublingual): One tablet dissolved under tongue or in the buccal pouch at the first sign of an acute angina attack; may repeat every 5 minutes up to 3 doses in a 15-minute period. May also use 1 tablet 5-10 minutes prior to activity Transdermal patch: 0.2-0.4	Pulmonary Hypertension: 0.25-0.5mcg/kg/minute and titrate by 1mcg/kg/min at 20-60 minute intervals; usual dose is 1-3mcg/kg/minute; maximum, 5mcg/kg/minute	Injection: 25 mg/250 ml 50 mg/10 ml 50 mg/250 ml 50 mg/500 ml 100 mg/250 ml 200 mg/500 ml Ointment: 2% Tablet (sublingual): 0.3 mg 0.4 mg 0.6 mg Transdermal patch: 0.2 mg/hr 0.3 mg/hr 0.4 mg/hr 0.6 mg/hr 0.8 mg/hr

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/hour, up to 0.8 mg/hour Translingual spray: 1-2 sprays onto or under tongue; no more than 3 sprays in a 15-minute period. May also use 1-2 sprays onto or under tongue 5-10 minutes prior to activity		Translingual spray: 0.4 mg/dose

SR=sustained-release

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Nitrates and Nitrites

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chronic Stable Angina				
Parker et al.[37] (1993) ISMN 5 mg BID vs ISMN 10 mg BID vs ISMN 20 mg BID vs placebo	DB, PC, PG Patients with stable angina underwent testing prior to exercise as well as 2 and 7 hours after each dose on days 1 and 14. Additionally, on days 7 and 21, testing was performed 2 hours after the first dose.	N=214 3 weeks	Primary: Total exercise duration and time to moderate angina	Primary: ISMN, at all doses, showed improvement over placebo at 2 and 7 hours after the morning dose and 2 hours after the second dose on day 1. Active treatment prolonged exercise duration over placebo at 2 hours postdose for each of the 2 daily doses. ISMN 20 mg was the only strength which demonstrated increased exercise duration 7 hours after administration, which occurred on day 14. Overall, there were fewer episodes of angina noted in the ISMN 20 mg group.
Thadani et al.[38] (1994) ISMN 20 mg BID vs placebo Patients were allowed to continue β-blocker therapy.	DB, MC, PC, PG, RCT Patients with stable exertional angina who stopped treadmill exercise secondary to angina pectoris	N=116 2 weeks	Primary: Total exercise duration (time to moderately severe angina) Secondary: ST-segment depression, heart rate, systolic and diastolic blood pressure, number of anginal attacks, number of nitroglycerin doses	Primary: A statistically significant improvement in total exercise duration was observed at both the morning and afternoon dose compared to placebo (P<0.01). Secondary: The magnitude of ST-segment depression was comparable in both the isosorbide-5-mononitrate and placebo groups (1.2±0.1 mm vs 1.2±0.2 mm; P>0.2). Heart rate and systolic blood pressure, during the period of exercise, was determined to be similar among the groups. Additionally, the number of anginal attacks and doses of nitroglycerin were no different per group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chrysant et al.[39] (1993) ISMN ER 30 mg QAM vs ISMN ER 60 mg QAM vs ISMN ER 120 mg QAM vs ISMN ER 240 mg QAM vs placebo	DB, RCT Patients with stable effort-induced angina	N=313 6 weeks	Primary: Mean change from baseline in total exercise time (serial exercise testing immediately prior to and 4 and 2 hours after administration, on days 1, 7, 14, 28 and 42) Secondary: Adverse effect	Primary: A significant improvement in mean total exercise time of 30 to 50 seconds was shown in all active-treatment groups compared to placebo at 4 and 12 hours postdose (P<0.01). The mean changes from baseline in total exercise time in patients on ISMN ER 120 mg or 240 mg surpassed placebo by about 50 to 60 seconds at 4 hours postdose (P<0.01), and by 30 to 35 seconds 12 hours after dosing (P≤0.05). There was no meaningful difference in response found between active treatment and placebo at 24 hours after administration, thus no indication that ISMN ER induced rebound angina. Secondary: The most common adverse effect among active treatment groups was transient headache.
Bray et al.[40] (1991) NTG administered buccally vs NTG administered sublingually	DB, MC Patients with proven chronic stable exercise-induced angina	N=Not reported Duration not reported	Primary: Efficacy	Primary: The two formulations had comparable effects on acute attacks of angina pectoris.
Ryden et al.[41] (1987)	MC, XO Patients with stable	N=126 2 weeks	Primary: Efficacy	Primary: Buccal nitroglycerin resulted in 31% less acute anginal attacks compared to the sublingual formulation (P<0.001). Prophylaxis was effective in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NTG administered buccally vs NTG administered sublingually	angina pectoris		Secondary: Ease of use, patient preference	74% of patients taking buccal nitroglycerin compared to 66% of sublingual-treated patients (P<0.05). Secondary: There was no difference in ease of use reported in 67% of patients, whereas 19% indicated that sublingual nitroglycerin was easier and 14% buccal nitroglycerin. Overall, 65% of patients preferred buccal nitroglycerin and 19% preferred sublingual nitroglycerin (P<0.05). As far as prophylactic use, buccal administration was again preferred by more patients (81%) than sublingual use (4%; P<0.05).
Demots et al.[42] (1989) NTG 0.2 mg/hour or 0.4 mg/hour TD for 12 hours (Group A) vs NTG 0.6 mg/hour or 0.8mg/hour TD for 12 hours (Group B) vs placebo	DB, RCT Patients with chronic stable angina	N=206 4 weeks	Primary: Effectiveness in chronic stable angina (serial treadmill testing performed 0, 4, 8 and 12 hours after patch application at baseline and on days 1, 15 and 29) Secondary: Adverse reaction	Primary: Improved walking times were observed in both Group A and Group B over placebo at all testing points after short-term administration. Results were statistically significant for Group A at 12 hours and for Group B at 4, 8 and 12 hours. At weeks 2 and 4, walking times were again greater in Group B over placebo at all testing points with the 4 hour test time at week 2 and the 8 hour test time at week 2 and 4 reaching statistical significance. Group A did not demonstrate increased duration in walking time long-term. Secondary: Active therapy was generally tolerated well. An increase in nonexertional angina during the patch-off interval was reported in 9 patients.
Ninomiya et al.[35] (2008) Isosorbide dinitrate SR 40 mg/day or isosorbide mononitrate SR 40 mg/day	RCT Patients suspected to have angina pectoris and with normal or mildly diseased coronary arteries underwent Doppler flow study	N=42 Not specified	Primary: Coronary wall shear stress Secondary: Changes in coronary blood flow	Primary: The percent increase in coronary blood flow and coronary artery diameter induced by acetylcholine was significantly smaller in the sustained-release nitroglycerin group than in the calcium channel blocker group (33% +/- 74% vs 83% +/- 77%, P<0.05; -3% +/- 16% vs 11% +/- 12%, P<0.01, respectively). Secondary: The percent diameter decrease in the region of greatest constrictive

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine 5mg/day or nifedipine ER 20 mg/day	of the left anterior descending coronary artery. All patients had been taking long acting nitrates or calcium channel blockers for at least 1 year			response to acetylcholine was significantly greater in the sustained-release nitroglycerin group than in the calcium channel blocker group (44% +/- 39% vs 15% +/- 32%, P<0.02).
Unstable Angina				
Dellborg et al.[43] (1991) NTG IV for 24 hours vs NTG administered buccally every 4 hours	RCT Patients admitted to the coronary care unit due to unstable angina	N=29 24 hours	Primary: Efficacy Secondary: Adverse effects	Primary: Efficacy was comparable in the two groups Secondary: Less adverse effects (headache, hemodynamic intolerance) were associated with buccal nitroglycerin than IV although the differences were not significant.
Kaplan et al.[44] (1983) NTG IV 10 mcg/min increased by 10 mcg/min every 5 minutes to 50 mcg/min then increased by 50 mcg/min per each episode of angina	OL, OS Patients with angina at rest unresponsive to standard therapy including oral or topical nitrates and β-blockers	N=35 24 hours	Primary: Clinical response	Primary: NTG therapy reduced the number of episodes of angina at rest from 3.5±0.4 to 0.3±0.1, reduced doses of sublingual nitroglycerin from 1.9±0.3 to 0.4±0.1 mg/day and decreased morphine sulfate use from 5.5±1.3 to 0.4±0.2 mg/day (P<0.001 for all). Complete response, defined as no rest angina, was achieved in 25 patients, while 8 patients experienced greater than a 50% reduction in episodes and 2 patients where nonresponders.
Karlberg et al.[45] (1998) NTG IV titrated from 1.5 mL/hour in <1 hour to a	DB, PC, RCT Patients with recent onset of chest pain, suggestive of myocardial	N=143 48 hours	Primary: Reduction in ongoing signs of myocardial ischemia, leukocyte	Primary: Treatment with nitroglycerin IV resulted in fewer patients (13) experiencing ongoing signs of ischemia (AP1 + AP2) than placebo (25; P<0.03). There were significantly less patients on active treatment that required >2 sublingual nitroglycerin tablets compared to placebo (12 vs 22; P<0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
maximum of 12 mL/hour vs placebo	ischemia or worsening of previously stable angina pectoris and clinical evidence of underlying coronary artery disease		activation, inhibition of platelet aggregation Secondary: Adverse effects	There was no significant difference found between groups in regards to leukocyte activation or inhibition of platelet aggregation. Secondary: Active treatment was stopped in 7 patients compared to 0 in the placebo group (P<0.001). Five patients terminated therapy prematurely because of headache while 2 patients stopped because of a decrease in blood pressure and bradycardia.
Heart Failure				
Cohn et al.[46] (1986) V-HeFT I ISDN 160 mg daily plus hydralazine 300 mg daily vs prazosin 20 mg daily vs placebo	AC, DB, PC, RCT Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic	N=642 3 years	Primary: Mortality Secondary: Effect on left ventricular function	Primary: There was a 34% risk reduction in mortality by 2 years in the ISDN plus hydralazine group compared to placebo (P<0.028). Cumulative mortality rates of 25.6% and 36.2% were observed in the ISDN plus hydralazine group at 2 and 3 years respectively, compared to 34.3% and 46.9% in the placebo group. The results found in the prazosin group were similar to placebo. Secondary: A significant increase in the left ventricular ejection fraction was reported at 8 weeks and 1 year in the ISDN plus hydralazine treatment group, but not in either the prazosin or placebo groups.
Cohn et al.[47] (1991) ISDN 40 mg QID and hydralazine 75 mg QID (individual agents, concurrent therapy)	AC, DB, RCT Men with heart failure (primarily NYHA class II and III), receiving digoxin and diuretics	N=804 2 years	Primary: All-cause mortality	Primary: The results demonstrated significantly lower mortality after 2 years with enalapril (18%) vs ISDN and hydralazine (25%; P=0.016). In addition, overall mortality tended to be lower with enalapril vs ISDN and hydralazine (P=0.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs enalapril 10 mg BID				
Taylor et al.[48] (2004) A-HeFT ISDN 20 mg plus hydralazine 37.5 mg TID increased to ISDN 40 mg plus hydralazine 75 mg TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for at least 3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 Mean duration of follow-up was 10 months	Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, quality of life changes	Primary: Combination of vasodilators in addition to standard therapy had significant mortality benefit (mortality rate of 6.2% vs 10.2%; P=0.02). From a range of possible scores of –6 to +2, patients in the active treatment group achieved a significantly better score of –0.1±1.9 compared to –0.5±2.0 in the placebo group (P=0.01). Each separate value of the composite score was also significantly better in the active group when compared to placebo. There was a 43% decrease in the rate of death from any cause (HR, 0.57; P=0.01), and a 33% reduction in the rate of first hospitalizations (P=0.001). This led to the early termination of the trial. Additionally, there was a significant improvement in quality of life scores found with ISDN plus hydralazine when compared to placebo (–5.6±20.6 vs –2.7±21.2; P=0.02).

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QAM=every morning, QID=four times daily, TD=transdermal, TID=three times daily
Study abbreviations: AC=active-controlled, DB=double-blind, HR=hazard ratio, MC=multicenter, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations; A-HeFT=African-American Heart Failure Trial, ER=extended release, ISDN=isosorbide dinitrate, ISMN=isosorbide mononitrate, nitroglycerin=nitroglycerin, NYHA=New York Heart Association, V-HeFT=Vasodilator Heart Failure Trial

Additional Evidence

Dose Simplification
Kardas et al. evaluated adherence rates with once-daily isosorbide mononitrate compared to twice-daily isosorbide mononitrate over the course of 10 weeks.[49] Adherence rates were significantly better with the once-daily regimen compared to the twice-daily regimen (P<0.001). The once-daily regimen also led to a significant reduction in the mean weekly number of chest pain episodes compared to the twice-daily regimen (P<0.0001). Brun et al. evaluated adherence with a once-daily and twice-daily formulation of isosorbide mononitrate in patients with stable angina.[36] Adherence rates were better with the once-daily regimen compared to the twice-daily regimen. The improvement in adherence also resulted in fewer angina episodes and a reduction in the number of nitroglycerin tablets that were taken to treat acute angina attacks.

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 branded products with little or no recent utilization data, the average cost per prescription is calculated by the average wholesale price (AWP) and the standard daily dosing per product labeling. For generic products with little or no recent utilization data, the average cost per prescription is calculated by the Alabama Medicaid maximum allowable cost (MAC) and the standard daily dosage 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 Nitrates and Nitrites

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amyl nitrite	inhalant	N/A	N/A	$
Isosorbide dinitrate	sublingual tablet, sustained-release capsule, sustained-release tablet, tablet	Dilatrate-SR®, Isordil®*, Isordil Titradose®*	$$$	$-$$
Isosorbide mononitrate	sustained-release tablet, tablet	Imdur®*, Ismo®*, Monoket®*	$$$-$$$$	$
Nitroglycerin	injection, ointment, sublingual tablet, transdermal patch, translingual spray	Minitran®*, Nitro-Bid®*, Nitro-Dur®*, Nitrolingual®, Nitrostat®*, Nitromist®†	$-$$$$	$-$$

*Generic is available in at least one dosage form or strength.
†Product was added to Medicaid's drug file after the meeting's drug list was approved.
N/A=Not available

X. Conclusions

The nitrates and nitrites are approved for the acute, prophylactic and chronic treatment of angina.[1-14] In addition, intravenous nitroglycerin is approved for the control of congestive heart failure in the setting of myocardial infarction, for the induction of intraoperative hypotension, and for the treatment of perioperative hypertension. All of the nitrate and nitrite products are available in a generic formulation.
.
There are several organizations that provide recommendations on the use of the nitrates and nitrites. Sublingual nitroglycerin tablets and nitroglycerin spray are recommended for the immediate relief of angina in all patients. For the treatment of chronic angina, β-blockers are recommended as first-line therapy.[16,20-21,24,28,52] Long-acting calcium channel blockers or long-acting nitrates may be used if initial therapy is not successful, or if β-blockers are contraindicated.[16,20-21,24,28,52] Combination therapy may be necessary in certain patients. The combination of β-blockers and long-acting nitrates are preferred due to their efficacy and safety.[28] Nitrates have not demonstrated a reduction in mortality in patients with coronary artery disease or following a myocardial infarction.[20] Sublingual and intravenous nitroglycerin is recommended for the acute treatment of unstable angina, myocardial infarction and acute coronary syndrome in addition to standard therapy.[17-18,22-23,33] For the treatment of heart failure, ACE inhibitors, β-blockers and diuretics are the cornerstone of therapy.[15,25-27,29,32,34] The combination hydralazine and a nitrate is an alternative treatment option in patients with heart failure. This combination has been shown to improve survival compared to placebo, but is less effective than ACE inhibitors. It should not be used in patients who have no prior use of an ACE inhibitor, or substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty.[15,25,27,32] The addition of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an ACE inhibitor and β-blocker for symptomatic heart failure, but who have persistent symptoms.[15,25-27,32]

Since all nitrates have similar pharmacologic effects, product selection is based on the desired onset and duration of action. Tolerance develops after chronic exposure to nitrates, regardless of the route of administration or formulation used.[1-14] This can be overcome by instituting short periods (10-12 hours) of withdrawal from nitrate therapy.[1-14]

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

Therefore, all brand nitrates or nitrites 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 nitrate or nitrite 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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Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Dyslipidemia
August 11, 2010

I. Overview

Cholesterol is a non-water-soluble lipid which is transported through the bloodstream as part of a lipoprotein.[3] There are 3 main classifications of lipoproteins: low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very low-density lipoproteins (VLDL).[3] Epidemiological observations and over 4 decades of clinical trials have demonstrated a correlation between lowering of LDL cholesterol (LDL-C) and a reduced incidence of CHD and CHD mortality.[1-2,4-5] In 2002, this evidence was examined by the National Cholesterol Education Program (NCEP), part of the National Heart, Lung, and Blood Institute (NHLBI), in a comprehensive treatment guideline known as the Adult Treatment Panel (ATP) III.[4] This guideline identifies LDL-C, which accounts for 60% to 70% of total serum cholesterol, as the major atherogenic lipoprotein associated with CHD risk, and further specifies LDL-C as the primary target of cholesterol-lowering therapy. Among other lipid risk factors are elevated triglycerides (TG), non-HDL cholesterol (defined as VLDL+LDL), and low HDL cholesterol levels (HDL-C).[4]

Therapeutic intervention for the prevention of CHD considers multiple risk factors, one of which is elevated LDL-C levels. This approach takes into account the findings of the Framingham Heart Study, which evaluated the relationship between serum cholesterol levels and other factors contributing to the lifetime risk for the development of CHD.[6] An estimate of a patient's risk of developing CHD or experiencing a coronary event in the next 10 years can be calculated based on age, total cholesterol, HDL-C, systolic blood pressure, and smoking status.[6] Therefore, nonlipid risk factors associated with CHD risk should also be considered in preventive efforts.[4] Some risk factors, such as hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity, and atherogenic diet, are modifiable and are appropriate targets for intervention. The non-modifiable factors of advancing age, male sex, or a family history of premature CHD may signal the need for more intensive lowering of LDL-C. The NCEP ATP III guideline assigns therapeutic goals to individual patients depending upon risk level. This approach follows earlier guidelines from the NCEP and employs a system for assessing short-term (≤10 years) CHD risk, which was developed in the course of the Framingham Heart Study.[4,6]

Therapeutic lifestyle changes (TLC) are an essential modality in clinical management and consist of a multifactorial lifestyle approach to reducing risk for CHD. TLC may reduce cardiovascular risk through several mechanisms beyond LDL lowering, and they are recommended as initial therapy in all patients with lifestyle-related risk factors requiring lipid management, regardless of LDL level.[4,7] The use of TLC, including LDL-lowering dietary options, can achieve therapeutic LDL goals in many patients. TLC may also be important in the management of patients with the constellation of risk factors referred to as the metabolic syndrome.[8] This syndrome is characterized by the simultaneous presence of major metabolic risk factors for atherosclerotic cardiovascular disease (CVD), which include atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose.[4,9] These risk factors often lead to prothrombotic and pro-inflammatory states in affected individuals.[9] Metabolic syndrome increases the risk for CHD regardless of LDL-C level.[4] Contributing factors may include abdominal obesity, insulin resistance, physical inactivity, aging, hormonal imbalance, and an atherogenic diet, making TLC a priority for this population.[9]

If TLC alone fails to achieve target goals, consideration can be given to adding drug therapy.[4,7] The HMG-CoA reductase inhibitors (statins) are the only class of drugs that have demonstrated significant improvements in overall mortality in primary and secondary prevention.[11] As a result, statins are often the first choice for treating hyperlipidemia in which the goal is primary or secondary cardiovascular risk reduction. Statins are the most potent LDL-C lowering agents with LDL-C reductions ranging from 20% to 60%.[4,6,11] If desired LDL-C levels cannot be attained with the use of statin monotherapy, additional antilipemic agents are often added to the treatment regimen. The choice of an additional agent may be influenced by the presence of other lipid abnormalities in addition to LDL-C.

If TG levels are high, non-HDL cholesterol can serve as a secondary target of therapy.[4] If hypertriglyceridemia is the primary lipid abnormality, fibric acid derivatives are particularly effective. They are also effective for raising HDL-C levels. Overall, the fibric acid derivatives lower TG levels by 25%-50% and increase HDL-C by 10%-35%.[12] They may lower LDL-C in some patients, but when they decrease elevated TG, LDL-C may increase.[12] Niacin shares a similar lipid-lowering profile as the fibric acid derivatives and decreases TG by 20%-35% and increases HDL-C by 15%-35%. Total plasma and LDL-C may decrease by 5%-25%.[12] The use of niacin has been limited historically by poor tolerability.[11-13]

Cholesterol absorption inhibitors are most commonly used in combination with statins to maximize LDL-C lowering. This is particularly useful when circumstances preclude titration of a statin. Bile acid sequestrants are useful in instances of mild-to-moderate LDL-C elevation. The use of these agents, as with niacin, is often limited by poor tolerability. Omega-3 fatty acid esters are also a treatment option; however, their use is not routinely addressed in treatment guidelines.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of dyslipidemia are summarized in Table 1.

Table 1. Current Treatment Guidelines for Dyslipidemia

National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): Implications of Recent Clinical Trials for the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III Guidelines[7]
(2004)

- The goals of therapy are based on 3 categories of risk level for CHD:
  - Patients with CHD and "CHD risk equivalents" (see below)
  - Patients with multiple (2+) risk factors
  - Patients with 0 to 1 risk factor
- CHD risk equivalents include noncoronary forms of clinical atherosclerotic disease (abdominal aortic aneurysm, carotid artery disease, and peripheral arterial disease), diabetes and multiple (2+) CHD risk factors with a 10-year risk for CHD >20%.
- Persons with CHD are at very high risk for future CHD events (10-year risk >20%). CHD is defined here as a history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
- ATP III employs a system of calculating 10-year risk for CHD based upon the results and methodology of the Framingham Heart Study (and therefore known as "Framingham risk scoring"). The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL-C, systolic blood pressure, treatment for hypertension, and cigarette smoking. Persons whose Framingham risk calculation shows a 10-year risk for CHD of >20% are considered to have a CHD risk equivalent.
- ATP III uses an alternative approach to risk assessment for persons in lower risk categories (e.g., without CHD or CHD risk equivalents), which is to count the number of other major risk factors for CHD. The guideline recommends that the factors listed in the following table be used to establish the count of risk factors.

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals[13]	
Positive Risk Factors (Increase Risk for CHD; Add 1 to Count)	**Negative Risk Factors (Decrease Risk for CHD; Subtract 1 from Count)**
Cigarette smoking	
Hypertension (blood pressure 140/90 mm Hg or on antihypertensive medication)	
Low HDL-C (<40 mg/dL)	HDL-C ≥60 mg/dL
Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)	
Age (men ≥45 years; women ≥55 years)	

Lipid management should be guided according to the cutoff points outlined in the following table.

Therapy in Different Risk Categories			
Risk Category	**LDL-C Goal**	**LDL-C Level at Which to Initiate TLC**	**LDL-C Level at Which to Consider Drug Therapy***
High Risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)†	≥100 mg/dL‡	≥100 mg/dL (<100 mg/dL: consider drug options)§
Moderately High Risk: 2+ risk factors (10-year risk 10%-20%)	<130 mg/dL (optional goal: <100 mg/dL)	≥130 mg/dL‡	≥130 mg/dL (100-129 mg/dL: consider drug options)‖
Moderate Risk: 2+ risk factors (10-year risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower Risk: 0-1 risk factor¶	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-C-lowering drug optional)

*When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels.
†For very high-risk patients, an LDL-C goal of <70 mg/dL is favored, and in patients with high triglycerides, a non–HDL-C goal of <100 mg/dL is favored.
‡Any person at high risk or moderately high risk who has lifestyle-related risk factors is a candidate for TLC to modify these risk factors regardless of LDL-C level.
§If baseline LDL-C is <100 mg/dL, institution of an LDL-C-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.
‖For moderately high-risk persons, when LDL-C level is 100-129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.
¶Almost all people with 0-1 risk factor have a 10-year risk ≤10%, and 10-year risk assessment is not necessary.

Treatment

TLC remains an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.

Lipid Targets of Therapy

- LDL-C is identified as the primary target of lipid-lowering therapy.
- For every 1% reduction in LDL-C levels, the relative risk for major CHD events is reduced by approximately 1%.
- Non–HDL-C (VLDL+LDL-C) is a secondary target in patients with TG ≥200 mg/dL.
- The non–HDL-C goal is 30 mg/dL higher than the LDL-C goal (the normal VLDL is <30 mg/dL).
- The recent trials that were evaluated for this update provide no new evidence to warrant setting a specific goal for HDL-C.
- Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins.
- Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with statins.
- In high-risk patients with high TG or low HDL levels as the predominant lipoprotein abnormality, consideration can be given to combination therapy with fibrates or nicotinic acid and an LDL-C-lowering agent.
- When TG levels are ≥200 mg/dL, non–HDL-Cis a secondary target of therapy, with a goal 30 mg/dL higher than identified LDL-C goal.

High-Risk Patients

- High-risk patients are defined as in ATP III, and this category includes all patients with CHD or CHD risk

equivalents (noncoronary forms of clinical atherosclerotic disease, diabetes, and multiple [2+] CHD risk factors with 10-year risk for CHD >20%).

- The recommended LDL-C goal for high-risk patients was set in ATP III at <100 mg/dL; however, an LDL-C goal of <70 mg/dL can be a therapeutic option on the basis of available clinical evidence, especially for patients at very high risk.
- This update to the ATP III guideline establishes a subset of high-risk patients as "very high-risk." This includes all patients with established cardiovascular disease (CVD) plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high TG ≥200 mg/dL in addition to non–HDL-C≥130 mg/dL with low HDL-C [<40 mg/dL]), and (4) acute coronary syndromes (on the basis of PROVE-IT).
- The cutoff point for considering drug therapy in all high-risk patients has been lowered from ≥130 mg/dL in ATP III to ≥100 mg/dL in this update.
- When LDL-C-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction.
- Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols).
- When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals.
- If a high-risk person has high TG or low HDL-C levels, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When TG are >200 mg/dL, non–HDL-Cis a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- In all high-risk patients, if baseline LDL-C level is ≥130 mg/dL, LDL-lowering agents should be started simultaneously with dietary therapy.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated TG, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.

<u>Moderately High-Risk Patients</u>

- Moderately high-risk patients are those with 2+ risk factors and a 10-year CHD risk of 10%-20%.
- Their recommended LDL-C goal remains <130 mg/dL; however, an LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical evidence.
- When LDL-C level is 100-129 mg/dL, at baseline or on TLC, initiation of an LDL-lowering drug to achieve an LDL-C level ≤100 mg/dL is a therapeutic option on the basis of available clinical evidence.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction.
- Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols).
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.

<u>Moderate-Risk Patients</u>

- Moderate-risk patients are those with 2+ risk factors and a 10-year CHD risk of <10%.
- The LDL-C goal for them remains at <130 mg/dL, as in the ATP III guideline.
- If LDL-C is ≥160 mg/dL after an adequate trial of dietary therapy, consideration should be given to adding

a cholesterol-lowering agent.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cut points of therapy as presented in the ATP III guideline.

Lower-Risk Patients

- Lower-risk patients are those with 0-1 risk factor.
- The LDL-C goal for them remains at <160 mg/dL, as in the ATP III guideline.
- If LDL-C is ≥190 mg/dL after an adequate trial of dietary therapy, consideration should be given to adding a cholesterol-lowering agent.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cut points of therapy as presented in the ATP III guideline.

Familial Disorders That Cause Very High LDL-C Levels (≥190 mg/dL)

Heterozygous Familial Hypercholesterolemia

- Begin LDL-C-lowering drugs in young adulthood
- TLC indicated for all persons.
- Statins: first line of therapy (start dietary therapy simultaneously)
- Bile acid sequestrants (if necessary in combination with statins)
- If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid)

Homozygous Familial Hypercholesterolemia

- Dietary therapy not effective
- Bile acid sequestrants not effective
- Nicotinic acid mildly effective
- Statins may be moderately effective in some persons
- Ileal exclusion operation not effective
- Liver transplant effective, but impractical
- LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia)

Familial Defective Apolipoprotein B-100

- TLC indicated
- All LDL-C-lowering drugs are effective
- Combined drug therapy required less often than in heterozygous FH

Polygenic Hypercholesterolemia

- TLC indicated for all persons
- Consider for drug therapy (if LDL-C ≥190 mg/dL after dietary therapy [all persons])
- All LDL-C-lowering drugs are effective
- If necessary to reach LDL-C goals, consider combined drug therapy

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)[4] (2002)

General Recommendations

- Initiate LDL-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid.
- After 6 weeks if LDL goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid.

- After 6 weeks, if LDL goal is not achieved, intensify drug therapy or refer patient to a lipid specialist. If LDL goal is not achieved, treat other lipid risk factors.
- After 4-6 months, monitor response and adherence to therapy.

Specific Drug Regimens

Bile Acid Sequestrants

- Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, and for persons needing only modest reductions in LDL cholesterol to achieve target goals.
- Bile acid sequestrants should be considered in combination therapy with statins in persons with very high LDL cholesterol levels.

Fibric Acid Derivatives

- Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis.
- They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL).
- Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia.
- They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.

HMG-CoA Reductase Inhibitors (Statins)

- Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

Nicotinic Acid

- Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia.
- Nicotinic acid should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a sustained increase in LDL levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL levels.
- Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia and gout, and type 2 diabetes.
- High doses of nicotinic acid (>3 grams/day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia.

Omega-3 Fatty Acids

- Omega-3 fatty acids (linolenic acid, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) have 2 potential uses.
- In higher doses, DHA and EPA lower serum TG by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3-12 grams/day have been used depending on tolerance and severity of hypertriglyceridemia.
- Recent clinical trials also suggest that relatively high intakes of omega-3 fatty acids (1-2 grams/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive clinical trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1-2 grams/day) for either primary or secondary prevention.

Other

- Cholesterol absorption inhibitors are not mentioned in this guideline.
- Hormonal replacement therapy cannot be recommended for the express purpose of preventing CHD.

Instead, control of risk factors should be the primary approach to reducing CHD risk in women. There may be other valid reasons for hormonal replacement therapy, such as for management of perimenopausal and postmenopausal symptoms or for treatment or prevention of osteoporosis.

European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice[28]
(2007)

Management

- Patients should be evaluated for exclusion of hyperlipidemias secondary to other conditions, since often the treatment of underlying disease improves hyperlipidemia.
- Patients with atherosclerotic disease and those at high risk for atherosclerotic disease should follow a diet designed to reduce cardiovascular risk and be engaged in physical exercise.
- Patients can be considered for drug therapy.
- Plasma lipids should be evaluated at baseline and again at 4-6 weeks and 3 months following an acute event and/or initiation of lipid-lowering therapy.

Cholesterol goals, general:
- <5 mmol/L (190 mg/dL), total
- <3 mmol/L (115 mg/dL), LDL

Cholesterol goals, patients with atherosclerotic disease and diabetes:
- <4.5 mmol/L (~175 mg/dL), total; <4 mmol/L (~155 mg/dL), total if feasible
- <2.5 mmol/L (~100 mg/dL), LDL; <2 mmol/L (~80 mg/dL), total if feasible

Drug Therapy

Statins
- HMG-CoA reductase inhibitors (statins) are considered first-line drugs for lowering LDL cholesterol.
- When TG are between ~450-900 mg/dL, statins (or fibrates) may be considered as first-choice drugs.

Fibric Acid Derivatives
- Fibric acid derivatives are considered useful only for the treatment of patients with low HDL, high TG, and other characteristics of insulin resistance syndrome and type 2 diabetes.
- Fibrate monotherapy cannot be recommended as first-line therapy in diabetic patients but may be considered in those with persistently low HDL levels or severely elevated TG.
- When TG are between ~450-900 mg/dL, fibrates (or statins) may be considered as first-choice drugs.

Bile Acid Sequestrants
- Bile acid sequestrants can serve as effective lipid-lowering alternatives.
- Bile acid sequestrants tend to increase TG; should only be used when TG are <~180 mg/dL or given in conjunction with TG-lowering agents.

Niacin
- Niacin is more effective at increasing HDL levels than fibrates.
- When TG are between ~450-900 mg/dL, either fibrates or statins may be used as first-line drugs, and niacin is a good drug and can serve as an effective lipid-lowering alternative in selected patients.

Cholesterol Absorption Inhibitors
- As monotherapy, cholesterol absorption inhibitors have mild LDL-lowering effects and can be used for patients with active liver disease, having adverse effects on statins or when statins, fibrates and nicotinic acid are contraindicated.
- Their primary role in therapy is in combination with statins.
- Cholesterol absorption inhibitors have not shown in clinical trials to reduce myocardial infarction and

coronary death.

Combination Therapy
- Combination therapy may be used in patients needing additional therapy to reach goals.
- The selection of appropriate drugs should vary based upon lipid levels.

American College of Cardiology (ACC)/American Heart Association (AHA)/National Heart, Lung, and Blood Institute: AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Disease: 2006 Update: Endorsed by the National Heart, Lung, and Blood Institute[25] (2006)

General Recommendations

- Two new trials published since the 2004 ATP III update demonstrated cardiovascular benefit for lowering LDL-C to <100 mg/dL for all patients with CHD and other clinical forms of atherosclerotic disease; additionally, an LDL-C level of <70 mg/dL is reasonable in these patients.
- For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP Panel III guidelines and their 2004 update should still be considered current.

Established Coronary or Atherosclerotic Disease

- Start dietary therapy, reducing the intake of saturated fats, trans-fatty acids, and cholesterol.
- Consider adding plant stanol/sterols and viscous fiber.
- Promote daily physical activity and weight management.
- Encourage increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 gram/day) for risk reduction.
- The goal of lipid management is an LDL-C <100 mg/dL. If TG are ≥200 mg/dL, non–HDL-C should be <130 mg/dL.

Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Lipid Management in Adults[26] (2009)

Lipid Management Algorithm

Step 1:
- Consider secondary causes of abnormal lipid levels and treat if appropriate.
- Patients with a history of non-coronary atherosclerosis (including carotid occlusive vascular disease, abdominal aortic aneurysm, or peripheral vascular disease) or who have diabetes are at high risk for CHD and are considered CHD risk equivalent.

Step 2:
- Diet and exercise are recommended as the cornerstone of treatment for asymptomatic patients with dyslipidemia.
- Lifestyle modifications may include the following: diet, aerobic exercise, weight management, evaluation of alcohol consumption, fish oil (EPA-DHA), smoking cessation, and a nutritional supplement containing sitostanol ester, a saturated derivative of a (EPA-DHA).
- Vitamin E supplements should not be used.

Step 3:
- Calculation of risk is based upon the National Cholesterol Education Program Adult Treatment Panel III guidelines. Once risk level is calculated, proceed to step 8.
- Step 4: If the patient has 0-1 risk factors and their 10-year CHD risk is <10%, then the LDL goal is <160 mg/dl. Consider drug therapy if the LDL is >190 mg/dl (optional if LDL is 160-189 mg/dl).
- Step 5: If the patient has 2+ risk factors and a 10-year CHD risk <10%, then the LDL goal is <130 mg/dl. Consider drug therapy if the LDL is >160 mg/dl (optional if LDL is 130-159 mg/dl).
- Step 6: If the patient has 2+ risk factors and a 10-year CHD risk of 10-20%, then the LDL goal is <100

mg/dl. Initiate drug therapy if the LDL is >130 mg/dl (optional if LDL is 100-129 mg/dl).

- Step 7: If the patient has CHD or a CHD risk equivalent and/or a 10-year risk >20%, then the LDL goal is <100 mg/dl. For patients with CHD, consider LDL goal <70 mg/dl. Initiate statin therapy and establish LDL goals.

Step 8:

- The decision to initiate and continue drug therapy should be made jointly by the patient and physician based on risk status.
- No primary prevention studies have addressed pharmacologic lipid treatment in persons at low risk for CHD, and there is no evidence to support drug treatment in this population. The incidence of CHD in men <40 and premenopausal women is very low, and drug treatment in these groups is discouraged. Primary prevention studies of pharmacologic lipid lowering have not shown a decrease in mortality, although most studies have shown about a 30% reduction in CHD events.
- Patients with risk factors for coronary heart disease but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of coronary heart disease.
- Patients with a history of coronary disease benefit from treatment with a statin. For patients with established CHD or CHD risk equivalent, the use of a statin is recommended. The specific statin and dose should be selected based the amount of lipid-lowering required. If patients are not able to tolerate a statin, clinicians are encouraged to have the patients try the other statins in reduced doses before ruling out all statins. If patients are still unable to take a statin, then bile-acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.

Step 9:

- If lipid goals are not met, intensify therapy until goals are reached.

Step 10:

- Potential adherence should be identified and then addressed by assessing the patient's knowledge of his/her medication(s) and condition, the patient's medication administration process, and the patient's barriers to adherence.
- Reinforce lifestyle modifications.

Step 11:

- If HDL is >40 mg/dL and triglycerides are <200 mg/dl, proceed to Step 12.
- If HDL is <40 mg/dL and triglycerides are >200 mg/dl, proceed to Step 14.

Step 12:

- A fasting lipid panel or lipid panel with direct LDL and transaminase should be obtained as indicated.

Step 13:

- Periodic monitoring, risk factor modification, and reinforcement of adjunctive measures are recommended.

Step 14:

- Patients with elevated triglyceride (TG) levels and normal or moderately elevated cholesterol should be treated if there is evidence of cholesterol-rich VLDL and intermediate-density lipoproteins (IDL).
- If TG are >500 mg/dL, TG-lowering drugs become first-line therapy. Statin therapy may also be considered especially if there is a strong family history of CHD and dyslipidemia or if the patient has evidence of atherosclerotic disease.
- Patients with TG >1,000 mg/dL are at an increased risk of hepatic steatosis, hepatomegaly, pancreatitis and splenomegaly and are candidates for dietary and drug therapy. If potential secondary causes have been addressed, the National Institutes of Health recommend dietary measures for initial management of borderline and high TG. If lifestyle modifications alone do not reduce TG to the desired level, then drug therapy is indicated. Treatment is also suggested in patients with diabetes whether or not they have low HDL cholesterol.
- Glucose levels should be controlled in diabetic patients since uncontrolled glucose levels contribute to hypertriglyceridemia.
- Non-HDL-cholesterol becomes a secondary target when triglycerides are 200-499 mg/dl. The non-HDL

target is 30 mg/dL higher than the LDL target.

Step 15:

- Adults with elevated lipids should follow the therapeutic lifestyle change or another equivalent diet (refer to Step 2).

Step 16:

- Coronary risk status and a lipid panel should be obtained at least annually.

Primary and Secondary Treatments for Dyslipidemia

Type of Dyslipidemia	Primary Therapy	Secondary Therapy
LDL ↑, HDL ≥40 mg/dL, TG >200 mg/dL	Weight loss Physical activity Discontinue smoking No alcohol Improve diabetes mellitus control Therapeutic lifestyle change	Statin Niacin* Omega-3 fatty acids
LDL ↑, HDL <40 mg/dL, TG >200 mg/dL		Statin Fibric acids Niacin* Omega-3 fatty acids Ezetimibe
LDL ↑, HDL ≥40 mg/dL	Weight loss Physical activity Therapeutic lifestyle change Discontinue smoking	Statin Fibric acids Niacin* Ezetimibe Bile acid sequestrant
LDL ↑, HDL <40 mg/dL		Statin Fibric acids Niacin* Bile acid sequestrant Ezetimibe
LDL normal, HDL <40 mg/dL	Physical activity Discontinue smoking	Fibric acids*** Statin Niacin* (Note: drug recommendations for treatment remain controversial except in CHD.)
TG ↑	Weight loss Discontinue smoking No alcohol Improve diabetes mellitus control Therapeutic lifestyle change Physical activity	Fibric acids Niacin* Omega-3 fatty acids

*Niacin can elevate glucose in patients with diabetes.
*** Although not FDA-labeled, use of gemfibrozil is supported by the VA-HIT Study.

General Treatment Recommendations

- Reducing LDL-C is the primary approach to lowering risk of CHD in both primary and secondary prevention. In some patients, triglycerides may be elevated along with LDL-C, so reducing triglycerides and increasing HDL-C may also be desirable.
- Selection of drug therapy is dependent on several factors including lipoprotein levels and percent reduction needed to attain goal; concurrent drug therapies that could increase the risk of side effects occurring with specific lipid-lowering drugs; and presence of other medical disorders that may affect drug metabolism, increase risk of side effects or be adversely affected by a specific lipid-lowering drug.
- For monotherapy, statins are the drugs of choice for lowering LDL.
- If patients are unable to take statins, then bile-acid sequestrants, ezetimibe, fibric acids and niacin can be used.

- Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it.
- Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile-acid sequestrant, with fewer side effects.
- In very resistant cases, triple therapy may be needed.

National Institute for Health and Clinical Excellence (NICE): Lipid Modification[29]
(2008)

General Treatment Recommendations

- Lifestyle modifications should include the following: diet, physical activity, weight management, evaluation of alcohol consumption, and smoking cessation.
- People should not routinely be recommended to take omega-3 fatty acid supplements or plant sterols/stanols for the primary prevention of CVD.
- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a ≥20% 10-year risk of developing CVD.
- Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of CVD.
- Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of CVD. If statins are not tolerated, these treatments may be considered.
- The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of CVD.
- Statin therapy is recommended for adults with clinical evidence of CVD. People with acute coronary syndrome should be treated with a higher intensity statin.
- Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dl) or LDL-C <2 mmol/L (<77 mg/dl) is not attained.
- Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with CVD who are not able to tolerate statins.
- People with primary hypercholesterolemia should be considered for ezetimibe treatment.

American Heart Association (AHA): Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents [27]
(2007)

Original Recommendations of the NCEP Expert Panel

- Drug therapy should be considered in children ≥10 years of age (usually waiting for menarche in females) and following 6-12 months of fat- and cholesterol-restricted dietary management.
- Drug therapy should be considered if LDL level remains ≥190 mg/dL or ≥160 mg/dL with a positive family history of premature cardiovascular disease or the presence of ≥2 other risk factors following vigorous attempts to control these risk factors.
- Consider referral to specialized lipid center.
- Treatment goals: minimal, LDL <130 mg/dL; ideal, LDL <110 mg/dL.

Modifications to the NCEP Expert Panel

- If the patient is overweight and/or obese, a fasting lipid profile should be obtained. If lipid abnormalities are present, the patient should be screened for other aspects of the metabolic syndrome.
- For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line

treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime.

- For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age.
- Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.

American Heart Association (AHA)/American Stroke Association (ASA): Primary Prevention of Ischemic Stroke[30]
(2006)

General Treatment Recommendations

- Plasma lipids and lipoproteins (total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and lipoprotein[a]) affect the risk of ischemic stroke, but the exact relationships are still being clarified.
- Increasing levels of total cholesterol are associated with higher rates of ischemic stroke.
- Low HDL cholesterol is a risk factor for ischemic stroke in men, but more data are needed to determine its effect in women.
- Additional studies are needed to clarify the risk associated with lipoproteins in women and the effect of treatment in older persons (>70 to 75 years of age).
- Lipid-modifying medications can substantially reduce the risk of stroke in patients with coronary heart disease.
- The National Cholesterol Education Program (NCEP) III guidelines for the management of patients who have not had a cerebrovascular event and who have elevated total cholesterol or elevated non–HDL cholesterol in the presence of hypertriglyceridemia are endorsed.
- It is recommended that patients with known CAD and high-risk hypertensive patients even with normal LDL cholesterol levels be treated with lifestyle measures and a statin.
- Suggested treatments for patients with known CAD and low HDL cholesterol include weight loss, increased physical activity, smoking cessation, and possibly niacin or gemfibrozil.
- If the patient has 0-1 risk factors and their 10-year CHD risk is <10%, then the LDL-C goal is <160 mg/dl. Consider drug therapy if the LDL-C is ≥190 mg/dl (optional if LDL-C is 160-189 mg/dl).
- If the patient has 2+ risk factors and a 10-year CHD risk <10%, then the LDL-C goal is <130 mg/dl. Consider drug therapy if the LDL-C is ≥160 mg/dl.
- If the patient has 2+ risk factors and a 10-year CHD risk of 10-20%, then the LDL-C goal is <100 mg/dl. Initiate drug therapy if the LDL-C is ≥130 mg/dl (optional if LDL-C is 100-129 mg/dl).
- If the patient has CHD or a CHD risk equivalent and/or a 10-year risk >20%, then the LDL-C goal is <100 mg/dl. For patients with CHD, consider LDL-C goal <70 mg/dl. Initiate drug therapy if the LDL-C is ≥130 mg/dl (optional if LDL-C is 70-129 mg/dl).
- If the patient has elevated non-HDL-C and triglycerides ≥200 mg/dl, the goals are 30 mg/dl higher than the LDL-C goal. Treatment recommendations are the same as LDL-C with goals 30 mg/dl higher.
- For patients with low HDL-C (no consensus goal), consider niacin or a fibrate in high-risk individuals with HDL-C <40 mg/dL.
- For patients with elevated Lp[a] (no consensus goal), consider niacin (immediate- or extended-release formulation) in conjunction with glycemic control and LDL-C control.

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