Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
November 10, 2010

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Central Alpha-Agonists
AHFS Class 240816
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I. Overview

Drugs to treat hypertension are among the most frequently prescribed pharmacologic agents. The incidence of hypertension increases with age and the proper selection of an antihypertensive agent is an important issue.[1-2] While a multitude of neurohormonal, renal and vascular mechanisms have been proposed as contributors to hypertension, no specific cause can be assigned in most cases.[3-4] Antihypertensive agents are separated into broad classes depending on which aspect of blood pressure regulation they affect: sodium and water balance, the sympathetic nervous system, resistance from vascular smooth muscle, or the renin-angiotensin-aldosterone system (RAAS).[5] Most patients will require therapy with more than one agent to achieve adequate blood pressure control. When monotherapy fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen.

The central alpha-agonists are approved for the treatment of hypertension. They lower blood pressure primarily through stimulation of α_2-adrenergic receptors in the central nervous system (CNS).[3,9-16] This action inhibits sympathetic vasomotor centers, causing decreased sympathetic outflow from the CNS and an associated increase in vagal tone. Sympathetic activity is reduced while parasympathetic activity is increased. This leads to a reduction in total peripheral resistance, systolic and diastolic blood pressure, baroreceptor reflexes, heart rate and cardiac output.[3,9-16] Plasma renin activity is also affected by the central alpha-agonists, but the relationship between this and their hypotensive effects has not been fully elucidated. Chronic central alpha-agonist use is associated with sodium and fluid retention, which may require concomitant diuretic therapy.[3] Both clonidine and methyldopa are available in combination with a thiazide diuretic. Thiazide diuretics inhibit the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules.[9-11] This action leads to an increase in the urinary excretion of sodium and chloride.

The central alpha-agonists 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 September 2008.

Table 1. Central Alpha-Agonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Clonidine	tablet, transdermal patch	Catapres®*, Catapres-TTS®*	clonidine
Clonidine and chlorthalidone	tablet	N/A	clonidine and chlorthalidone
Guanabenz	tablet	N/A	guanabenz
Guanfacine	tablet	Tenex®*	guanfacine
Methyldopa	tablet	N/A	methyldopa
Methyldopa and hydrochlorothiazide	tablet	N/A	methyldopa and hydrochlorothiazide
Methyldopate	injection^	N/A	methyldopate

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
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 central alpha-agonists are summarized in Table 2. For a more comprehensive overview of the treatment of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Central Alpha-Agonists

Clinical Guideline	Recommendation(s)
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management[33] (2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • The use of central alpha-agonists was not addressed in this guideline.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[19] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either

Clinical Guideline	Recommendation(s)
	combination component, the combination is likely to be well tolerated.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[20] (2006)**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • The use of central alpha-agonists was not addressed in this guideline.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[1] (2004)**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-adrenergic blocking agents (β-blockers), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium-channel blocking agents (CCBs). This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators. • Thiazide diuretics are useful in slowing demineralization in osteoporosis.

Clinical Guideline	Recommendation(s)
	• Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[17] (2004)**	• If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • The use of central alpha-agonists was not addressed in this guideline.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension[18] (2003)**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors). • The use of central alpha-agonists was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans[22] (2003)**	• The use of central alpha-agonists was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[21] (2010)**	• Multiple drug therapy is generally required to achieve blood pressure goals. • During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they can cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the central alpha-agonists 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 Central Alpha-Agonists[9-16]

Indication	Clonidine	Clonidine/ Chlorthalidone	Guanabenz	Guanfacine	Methyldopa	Methyldopa/ HCTZ
Treatment of hypertension	✔ *	✔ †	✔ *	✔ *	✔	✔ †

HCTZ=hydrochlorothiazide
*Alone or in combination with other antihypertensive agents.
†This fixed combination drug is not indicated for the initial therapy of hypertension.

IV. Pharmacokinetics

The pharmacokinetic parameters of the central alpha-agonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Central Alpha-Agonists[9-16]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Clonidine	Oral: 75-100 TD: 60	20-40	Liver	Renal (40-60) Feces (22)	Oral: 12-16 TD: 6-20
Clonidine and chlorthalidone	Not reported	Not reported	Not reported	Not reported	Not reported
Guanabenz	75	90	Not reported	Feces (16)	6
Guanfacine	80	70	Liver	Renal (40-75)	17
Methyldopa	25-50	<15	Liver	Renal (45) Feces (30-50)	1.7
Methyldopa and hydrochlorothiazide	Not reported	Not reported	Not reported	Not reported	Not reported

TD=transdermal

V. Drug Interactions

Significant drug interactions with the central alpha-agonists are listed in Table 5.

Table 5. Significant Drug Interactions with the Central Alpha-Agonists[9]

Generic Name(s)	Significance Level	Interaction	Mechanism
Chlorthalidone, hydrochlorothiazide	1	Lithium	Thiazide diuretics may promote enhanced proximal tubular reabsorption of lithium leading to elevated serum concentrations. Thiazide diuretics may increase the therapeutic and toxic effects of lithium.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Chlorthalidone, hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia, hyperuricemia and hypotension.
Chlorthalidone, hydrochlorothiazide	2	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.
Clonidine	2	Beta-adrenergic blockers	The severity of rebound hypertension associated with abrupt withdrawal of clonidine may be greater in patients taking beta-adrenergic blockers. This combination has also been reported to cause paradoxical hypertension. The mechanism of this interaction is unknown.
Clonidine,	2	Tizanidine	An additive effect on alpha$_2$-

Generic Name(s)	Significance Level	Interaction	Mechanism
guanfacine, methyldopa			adrenergic receptors by tizanidine and central alpha-agonists may occur. The potential for symptomatic additive hypotension exists when tizanidine is coadministered with central alpha-agonists.
Clonidine	2	Tricyclic antidepressants	The antihypertensive effectiveness of clonidine may be decreased. Tricyclic antidepressants may also worsen the rebound reactions, such as hypertension and tachycardia, from abrupt clonidine withdrawal. The mechanism of this interaction is unknown.
Clonidine	2	Verapamil	Sinus bradycardia, AV block and severe hypotension may occur with coadministration of clonidine and verapamil. The mechanism of this interaction is unknown.
Guanfacine	2	Tricyclic antidepressants	Concomitant use of guanfacine and a tricyclic antidepressant may cause loss of blood pressure control by tricyclic antidepressant inhibition of central α_2-receptors.
Methyldopa	2	Iron salts	The gastrointestinal absorption of methyldopa may be decreased by iron salts. The metabolism of methyldopa may also be affected. Therefore, the pharmacologic effects of methyldopa may be decreased.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the central alpha-agonists are listed in Table 6. Abrupt discontinuation may cause nervousness, palpitations, headache, perspiration, nausea and agitation. In some cases, sudden discontinuation may cause potentially dangerous rebound hypertension.[9-11] The boxed warning for methyldopa/hydrochlorothiazide is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Central Alpha-Agonists[9-16]

Adverse Events	Clonidine Oral	Clonidine Transdermal	Clonidine/ Chlorthalidone	Guanabenz	Guanfacine	Methyldopa	Methyldopa/ Hydrochlorothiazide
Cardiovascular							
Angina	-	-	-	-	-	✔	✔
Arrhythmia	✔	-	-	<3	-	-	-
Atrioventricular block	✔	-	✔	-	-	-	-
Bradycardia	✔	-	-	-	≤3	✔	✔
Carotid sinus sensitivity	-	-	-	-	-	✔	✔
Chest pain	<1	-	-	<3	≤3	-	-
Congestive heart failure	✔	-	✔	-	-	✔	✔
Edema	-	-	-	<3	-	✔	✔
Electrocardiogram abnormalities	✔	-	✔	-	-	-	-
Hypotension	-	-	-	-	-	✔	✔
Myocarditis	-	-	-	-	-	✔	✔
Necrotizing angitis	-	-	-	-	-	-	✔
Orthostatic hypotension	3	-	3	-	-	✔	✔
Orthostasis	-	-	-	>5	-	-	-
Palpitations	✔	-	<1	<3	≤3	-	-
Pericarditis	-	-	-	-	-	✔	✔
Peripheral edema	-	-	-	-	-	>10	-
Reynaud's phenomenon	✔	-	✔	-	-	-	-
Syncope	✔	-	<1	-	-	<1	-
Tachycardia	✔	-	<1	-	-	-	-
Central Nervous System							
Agitation	✔	-	3	-	-	-	-
Amnesia	-	-	-	-	≤3	-	-
Anxiety	✔	-	-	<3	-	1-10	-
Ataxia	-	-	-	<3	-	-	-
Bell's palsy	-	-	-	-	-	✔	✔
Confusion	-	-	-	-	≤3	-	-
Delirium	✔	-	<1	-	-	-	-
Decreased mental acuity	-	-	-	-	-	✔	✔

Adverse Events	Clonidine Oral	Clonidine Transdermal	Clonidine/ Chlorthalidone	Guanabenz	Guanfacine	Methyldopa	Methyldopa/ Hydrochlorothiazide
Delusional perception	✔	-	-	-	-	✔	✔
Depression	✔	-	1	<3	≤3	1-10	✔
Dizziness	16	2	16	12-17	12-15	✔	✔
Drowsiness	33	12	33	39	-	1-10	-
Fatigue	4	6	4	-	2-10	-	-
Hallucinations	<1	-	<1	-	-	-	-
Headache	1	5	1	5	3-13	1-10	✔
Insomnia	5	2	5	-	≤3	-	-
Involuntary movements	-	-	-	-	-	✔	✔
Lightheadedness	-	-	-	-	-	✔	✔
Lethargy	-	3	-	-	-	-	-
Nervousness	3	1	3	-	-	-	-
Nightmares	✔	-	-	-	-	✔	✔
Paresthesia	✔	-	✔	-	-	✔	✔
Parkinsonism	-	-	-	-	-	✔	✔
Restlessness	✔	-	-	-	-	-	✔
Sedation	10	3	10	-	-	✔	✔
Sleep disturbances	✔	-	-	<3	-	-	-
Somnolence	-	-	-	20-50	5-39	-	-
Vertigo	-	-	✔	-	-	-	✔
Weakness	10	-	10	10	2-7	✔	✔
Dermatological							
Allergic contact sensitization	-	5	-	-	-	-	-
Alopecia	✔	-	<1	-	-	-	✔
Angioedema	✔	-	<1	-	-	-	-
Blanching	-	1	-	-	-	-	-
Burning	-	3	-	-	-	-	-
Contact dermatitis	-	19	-	-	-	-	-
Dermatitis	-	-	-	-	≤3	-	-
Edema	3	3	3	-	-	-	-
Erythema	-	15-50	-	<1	-	-	✔
Excoriation	-	3	-	-	-	-	-
Exfoliative dermatitis	-	-	-	-	-	✔	✔
Hives	✔	-	<1	-	-	-	-
Hyperpigmentation	-	5	-	-	-	-	-
Lupus-like syndrome	-	-	-	-	-	✔	✔
Morbilliform or macro papular eruptions	-	1	-	-	-	-	✔

Adverse Events	Clonidine Oral	Clonidine Transdermal	Clonidine/ Chlorthalidone	Guanabenz	Guanfacine	Methyldopa	Methyldopa/ Hydrochlorothiazide
Photosensitivity	-	-	✔	-	-	-	✔
Pruritus	7	15-50	7	<3	≤3	-	-
Purpura	-	-	✔	-	≤3	-	✔
Rash	✔	-	1	<3	-	✔	✔
Stevens Johnson syndrome	-	-	-	-	-	-	✔
Sweating	-	-	-	-	≤3	<1	-
Throbbing	-	3	-	-	-	-	-
Toxic epidermal necrolysis	-	-	✔	-	-	✔	✔
Urticaria	✔	<1	<1	-	-	-	✔
Vasculitis	-	-	✔	-	-	✔	✔
Vesiculation	-	7	-	-	-	-	✔
Endocrine and Metabolic							
Breast enlargement	-	-	-	-	-	✔	✔
Erectile dysfunction	✔	-	-	-	-	-	-
Electrolyte imbalance	-	-	-	-	-	-	✔
Gynecomastia	✔	-	1	<3	-	✔	✔
Hyperprolactinemia	-	-	-	-	-	✔	✔
Impotence	3	2	3	<3	3-7	✔	✔
Lactation	-	-	-	-	-	✔	
Pancreatitis	-	-	✔	-	-	✔	✔
Sexual dysfunction	3	2	3	<3	≤3	✔	✔
Sodium retention	-	-	-	-	-	<1	-
Weight gain	✔	-	1	-	-	-	-
Gastrointestinal							
Abdominal Pain	✔	-	<1	<3	≤3	-	-
Anorexia	1	-	1	-	-	-	✔
Colitis	-	-	-	-	-	✔	✔
Constipation	10	1	10	<3	2-15	✔	✔
Cramping	-	-	-	-	-	-	✔
Diarrhea	-	-	✔	<3	≤3	✔	✔
Distention	-	-	-	-	-	✔	✔
Dry mouth	40	25	40	28-38	10-54	1-10	✔
Dry throat	-	2	-	-	-	-	-
Dyspepsia	-	-	-	-	≤3	-	-
Dysphagia	-	-	-	-	≤3	-	-
Flatus	-	-	-	-	-	✔	✔
Gastritis	-	-	✔	-	-	-	✔

Adverse Events	Clonidine Oral	Clonidine Transdermal	Clonidine/ Chlorthalidone	Guanabenz	Guanfacine	Methyldopa	Methyldopa/ Hydrochlorothiazide
Nausea	5	1	5	<3	≤3	✔	✔
Pseudo-obstruction	✔	-	-	-	-	-	-
Parotitis	✔	-	✔	-	-	-	-
Salivary gland pain	✔	-	-	-	-	-	-
Sialadenitis	-	-	-	-	-	✔	✔
Sore tongue	-	-	-	-	-	✔	✔
Taste alteration	-	1	-	<3	≤3	-	-
Vomiting	5	-	5	<3	-	✔	✔
Weight gain	1	-	1	-	-	✔	✔
Genitourinary							
Glucosuria	-	-	✔	-	-	-	✔
Interstitial nephritis	-	-	-	-	-	-	✔
Micturition difficulties	✔	-	<1	-	-	-	-
Nocturia	✔	-	1	-	-	-	-
Polyuria	-	-	-	<3	-	-	-
Renal dysfunction	-	-	-	-	-	-	✔
Renal failure	-	-	-	-	-	-	✔
Testicular disorder	-	-	-	-	≤3	-	-
Urinary incontinence	-	-	-	-	≤3	<1	-
Urinary retention	1	-	<1	-	-	-	-
Hematologic							
Agranulocytosis	-	-	✔	-	-	-	✔
Aplastic anemia	-	-	✔	-	-	-	✔
Bone marrow depression	-	-	-	-	-	✔	✔
Eosinophilia	-	-	-	-	-	✔	✔
Granulocytopenia	-	-	-	-	-	✔	✔
Hemolytic anemia	-	-	-	-	-	✔	✔
Leukopenia	-	-	✔	-	-	✔	✔
Positive antinuclear antibody test	-	-	-	-	-	✔	✔
Positive Rheumatoid factor test	-	-	-	-	-	✔	✔
Positive Coombs test	✔	-	✔	-	-	✔	✔
Thrombocytopenia	✔	-	<1	-	-	✔	✔
Hepatic							
Cholestasis	-	-	-	-	-	<1	-
Cirrhosis	-	-	-	-	-	<1	-
Hepatitis	✔	-	<1	-	-	✔	✔
Jaundice	-	-	✔	-	-	✔	✔

Adverse Events	Clonidine Oral	Clonidine Transdermal	Clonidine/ Chlorthalidone	Guanabenz	Guanfacine	Methyldopa	Methyldopa/ Hydrochlorothiazide
Laboratory Test Abnormalities							
Blood urea nitrogen increased	-	-	-	-	-	✔	✔
Electrolyte disturbance	-	-	-	-	-	-	✔
Creatinine phosphokinase increased	✔	-	✔	-	-	-	-
Hyperglycemia	✔	-	✔	-	-	-	✔
Hyperuricemia	-	-	✔	-	-	-	✔
Liver function test abnormalities	✔	-	1	-	-	✔	✔
Musculoskeletal							
Arthralgia	-	-	-	-	-	✔	✔
Hypokinesia	-	-	-	-	≤3	-	-
Leg cramps	✔	-	<1	-	≤3	-	-
Muscle spasms	-	-	✔	-	-	-	✔
Myalgia	✔	-	<1	<3	-	✔	-
Respiratory							
Dyspnea	-	-	-	<3	≤3	<1	✔
Respiratory distress	-	-	-	-	-	-	✔
Rhinitis	-	-	-	-	≤3	-	-
Other							
Anaphylaxis	-	-	-	-	-	-	✔
Blurred vision	✔	-	<1	<3	-	-	✔
Dry eyes	✔						
Conjunctivitis	-	-	-	-	≤3	-	-
Drug fever	-	-	-	-	-	1-10	✔
Fever	✔	-	-	-	-	-	✔
Iritis	-	-	-	-	≤3	-	-
Malaise	1	-	1	-	≤3	-	-
Nightmares	<1	-	<1	-	-	-	-
Paresis	-	-	-	-	≤3	-	-
Paresthesia	-	-	✔	-	≤3	-	-
Tinnitus	-	-	-	-	≤3	-	-
Vision disturbance	-	-	-	-	≤3	-	-
Withdrawal syndrome	✔	-	1	-	-	-	-
Xanthopsia	-	-	✔	-	-	-	✔

✔ Percent not specified
\- Event not reported

Table 7. Boxed Warning for Methyldopa/Hydrochlorothiazide[9]

WARNING
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

VII. Dosing and Administration

The usual dosing regimens for the central alpha-agonists are listed in Table 8.

Table 8. Usual Dosing Regimens for the Central Alpha-Agonists[9-16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Clonidine	Hypertension: Tablet: initial, 0.1 mg twice daily; maintenance, 0.1 to 0.6 mg/day in 2 divided doses; maximum, 2.4 mg/day Transdermal: initial, 0.1 mg patch once weekly; maintenance, 0.1 to 0.3 mg patch once weekly; maximum, 2 of the 0.3 mg patches once weekly	Safety and effectiveness in pediatric patients have not been established in adequate and well-controlled trials.	Tablet: 0.1 mg 0.2 mg 0.3 mg Transdermal patch: 0.1 mg/24 hours 0.2 mg/24 hours 0.3 mg/24 hours
Clonidine and chlorthalidone	Hypertension: Initial, 0.1 mg/15 mg one to two times daily; maintenance, 0.2 mg/15 mg one to two times daily; maximum, 0.3 mg/15 mg two times daily	Safety and efficacy in children have not been established.	Tablet: 0.1 mg/15 mg 0.2 mg/15 mg 0.3 mg/15 mg
Guanabenz	Hypertension: Initial, 4 mg twice daily; maintenance, 8 to 32 mg twice daily; maximum, 32 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 4 mg 8 mg
Guanfacine	Hypertension: Initial, 1 mg once daily at bedtime; maintenance, 1 to 2 mg once daily; maximum, 3 mg once daily	Safety and efficacy in children under 12 have not been established.	Tablet: 1 mg 2 mg
Methyldopa	Hypertension: Initial, 250 mg 2 to 3 times daily; maintenance, 500 to 2,000 mg daily in 2 divided doses; maximum dose, 3 g daily	There are no well-controlled clinical trials in pediatric patients. Information on dosing in pediatric patients is supported by evidence from published literature regarding the treatment of hypertension in pediatric patients. Hypertension: Initial, 10 mg/kg/day in 2 to 4 divided doses, then titrate up or down until adequate response achieved;	Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		maximum, 65 mg/kg/day or 3 g daily, whichever is less	
Methyldopa and hydrochlorothiazide	Hypertension: The usual starting dosage is 250 mg/15 mg two or three times a day or 250 mg/25 mg two times a day; maximum, hydrochlorothiazide 50 mg and methyldopa 3 g daily. Dosage must be individualized, as determined by titration of the individual components. Once the patient has been successfully titrated, methyldopa-hydrochlorothiazide may be substituted if the previously determined titrated doses are the same as in the combination.	Safety and efficacy in children have not been established.	Tablet: 250 mg/15 mg 250 mg/25 mg

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VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the central alpha-agonists are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Central Alpha-Agonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Weber et al.[32] (1983) Chlorthalidone 15 and clonidine 0.1 fixed-dose combination administered QD to BID vs placebo	DB, PC, RCT Men >60 years old with isolated systolic hypertension (supine SBP ≥160 mm Hg and DBP ≤100 mm Hg)	N=24 12 weeks	Primary: Blood pressure lowering efficacy Secondary: Adverse effects	Primary: SBP dropped significantly in both the supine and upright postures in the active treatment group (P<0.001). No significant change in the placebo group. DBP dropped significantly in both the supine and upright postures in the active group (P<0.05). No significant change in the placebo group. Secondary: Active treatment induced small decreases in potassium and small increases in uric acid levels (P<0.01) and induced an increase in the aldosterone excretion rate (P<0.05). However, no significant changes in creatinine clearance.
Rosenman et al.[24] (1975) Chlorthalidone and clonidine QD (doses not reported)	OL, RCT Patients with essential hypertension	N=30 2 years	Primary: Blood pressure lowering efficacy Secondary: Adverse effects	Primary: Patients on combination therapy experienced 12.9% to 16.4% enhanced blood pressure lowering effect vs patients on diuretic monotherapy. Secondary: Side effects were mild and mainly included dry mouth and drowsiness. Orthostatic hypotension was seen in 3 patients receiving combination therapy; however, it was relatively mild and subsided upon dose adjustment.
Lilja M et al.[28] (1991) Clonidine 0.1 mg tablets BID plus placebo vs clonidine 0.2 mg	DB, DD, PC, RCT, XO Patients with mild to moderate hypertension	N=16 12 weeks	Primary: Change from baseline in supine and standing SBP and heart rate Secondary: Difference in primary endpoints between oral and	Primary: Transdermal clonidine reduced both SBP and DBP by 13/7 mm Hg (P<0.01 and P<0.01) and heart rate by 9 beats/min (P<0.01) in the supine position. Oral clonidine produced a statistically significant reduction 11 mm Hg (P<0.01) only in supine SBP. In a standing position, transdermal clonidine reduced SBP and DBP by 14 to 9 mm Hg (P<0.01/0.01) and heart rate by 9 beats/min (P<0.01). Oral clonidine reduced only the standing heart rate to a statistically significant extent 8 beats/min (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
transdermal patch QD plus placebo			transdermal clonidine	Secondary: There were no differences reported in primary endpoints between transdermal and oral clonidine.
Houston et al.[25] (1993) Clonidine transdermal 0.1 to 0.3 mg QD plus nifedipine 60 mg QD (single entity products) vs nifedipine 60 mg QD plus placebo	OL, prospective, PC Male and nonpregnant female patients between 18 and 75 years of age with mild to moderate hypertension and inadequate response to nifedipine	N=42 8 weeks	Primary: Change in seated DBP to less than 90 mm Hg at 8 weeks	Primary: Patients on combination therapy experienced a reduction of 16/14 mm Hg in the mean seated blood pressure vs placebo (P<0.01) with mean seated blood pressure of 127/87 mm Hg. A reduction of 5/10 mm Hg in the mean seated blood pressure was seen with combination therapy vs nifedipine monotherapy (P<0.01). A reduction of 18/12 mm Hg in the mean standing blood pressure was seen with combination therapy vs placebo (P<0.01). A reduction of 9/9 mm Hg in the mean standing blood pressure was seen with combination therapy vs nifedipine monotherapy (P<0.01).
Kluyskens et al.[26] (1980) Guanabenz (mean dose 24 mg QD) vs clonidine (mean dose 0.45 mg QD)	DB, PC Non-pregnant patients 21 to 64 years of age with mild to moderate hypertension	N=29 8 weeks	Primary: Reduction in DBP between 5 to 10 mm Hg based on patients' pretreatment values	Primary: Both treatments resulted in statistically significant reductions in SBP and DBP from baseline and placebo periods (P<0.001).
McCarron[27] (1984) Guanabenz 16 to 31 mg QD vs HCTZ 50 to 75 mg	DB, MC, RCT Patients with mild to moderate hypertension	N=147 6 months	Primary: Change in supine DBP Secondary: Side effects	Primary: Patients in both the guanabenz and hydrochlorothiazide groups demonstrated a significant decreases in supine DBP (P<0.001). Secondary: Mild side effects (dry mouth, drowsiness) were reported more frequently (P<0.01) in the guanabenz-treated group vs the HCTZ group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD				
Boyles et al.[30] (1984) Methyldopa 250 to 800 mg/day and HCTZ 25 to 100 mg/day vs HCTZ 25 to 100 mg/day	OL, RCT Patients ≥59 years with isolated systolic hypertension	N=21 18 weeks	Primary: Changes in blood pressure from baseline	Primary: At 2 weeks standing blood pressure fell from a mean of 166/90 mm Hg at baseline to 164/88 mm Hg with HCTZ monotherapy. At 4 weeks standing blood pressure fell from a mean of 164/88 mm Hg at the end of the 2-week HCTZ monotherapy period to 145/811 mm Hg at 2 weeks with combination therapy. At 18 weeks standing blood pressure fell from a mean of 166/90 mm Hg at baseline to 132/80 mm Hg with combination therapy.
Channick et al.[31] (1981) Methyldopa 250 mg/day and HCTZ 15 mg/day vs chlorthalidone 50 mg/day and reserpine 0.25 mg/day	OL, RCT Patients with hypertension	N=56 12 weeks	Primary: Efficacy of blood pressure lowering to goal DBP ≤90 mm Hg Secondary: Adverse effects	Primary: Goal DBP of ≤90 mm Hg was reached in 91% of the chlorthalidone and reserpine group vs 55% in the methyldopa and HCTZ group (P<0.001). Secondary: The incidence of adverse effects was 31% with chlorthalidone and reserpine vs 64% with methyldopa and HCTZ (P<0.02).
Fernandez et al.[23] (1980) Methyldopa 750 mg/day vs chlorothiazide 450 mg/day	DB, PC, RCT, XO Patients with uncomplicated hypertension	N=44 4 weeks	Primary: Blood pressure Lowering efficacy Secondary: Adverse effects	Primary: No significant differences in supine blood pressures for any treatment arm vs placebo. However, upright SBP, DBP, and mean blood pressures were significantly lower after treatment with methyldopa or combination therapy vs treatment with placebo (P<0.05). Secondary: Adverse effects were reported as infrequent.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs methyldopa 250 mg and chlorothiazide 150 mg/day combination entity vs placebo				

Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: DB=double-blind, DD=double-dummy, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

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 10. Relative Cost of the Central Alpha-Agonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Clonidine	tablet, transdermal patch	Catapres®*, Catapres-TTS®*	$$$$-$$$$$	$-$$$$$
Clonidine and chlorthalidone	tablet	N/A	N/A	$$-$$$
Guanabenz	tablet	N/A	N/A	$$$-$$$$
Guanfacine	tablet	Tenex®*	$-$$	$
Methyldopa	tablet	N/A	N/A	$
Methyldopa and hydrochlorothiazide	tablet	N/A	N/A	$

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

X. Conclusions

The central alpha-agonists are approved for the treatment of hypertension, and all of the agents are available in a generic formulation.[9-16] There are several national and international organizations that have published guidelines on the treatment of hypertension.[1,17-22,33] Most of the guidelines do not address the use of the central alpha-agonists. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension. According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[19,33] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[19,33] All of the available guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use. Methyldopa and clonidine are safe and effective to use during pregnancy.[1,19,21]

There are limited head-to-head studies with the central alpha-agonists. Clinical trials have compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimen lowered systolic and diastolic blood pressure to a greater extent than the less-intensive treatment regimen.[25,30] There does not appear to be any difference in efficacy with the oral or transdermal formulations of clonidine.[28] Most patients will need more than one antihypertensive agent to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[19,33] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

The most common adverse events reported with the central alpha-agonists include dizziness, drowsiness, dry mouth and somnolence. Abrupt discontinuation may cause nervousness, palpitations, headache, perspiration, nausea and agitation. In some cases, sudden discontinuation may cause potentially dangerous rebound hypertension.[9-11]

There is insufficient evidence to support that one brand central alpha-agonist 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 central alpha-agonists 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 central alpha-agonist 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 Direct Vasodilators
AHFS Class 240820
November 10, 2010

I. Overview

The direct vasodilators are approved for the treatment of heart failure and hypertension, as well as for the treatment of hypoglycemia due to hyperinsulinism.[1-5] Hydralazine and minoxidil interfere with calcium movement within the vascular smooth muscle, which is responsible for initiating and maintaining the contractile state.[1-3] They exert a peripheral vasodilating effect through a direct relaxation of vascular smooth muscle. This leads to decreased arterial blood pressure, decreased peripheral vascular resistance, as well as an increase in heart rate, stroke volume and cardiac output.[1-3] Hydralazine is available as a single entity product, as well as in combination with isosorbide dinitrate. Isosorbide dinitrate enters vascular smooth muscle and is converted to nitric oxide, which results in dilatation of peripheral arteries and veins.[1-3] Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart. Dilation of the arteries reduces systemic vascular resistance, systolic arterial pressure and mean arterial pressure. The exact mechanism of action of the fixed-dose combination product containing isosorbide dinitrate/hydralazine in the treatment of heart failure has not been established.[5]

Diazoxide is a non-diuretic benzothiadiazine derivative taken orally for the management of symptomatic hypoglycemia.[4] It increases blood glucose levels by inhibiting the release of insulin from the pancreas, as well as by an extrapancreatic effect.[4] The hyperglycemic effect begins within an hour, generally lasts no more than 8 hours, and can be reversed by the administration of insulin or tolbutamide. The inhibition of insulin release by diazoxide is antagonized by alpha-adrenergic blocking agents.[4] The oral preparation does not demonstrate the same effects on blood pressure as the other direct vasodilators.

The direct vasodilators that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Hydralazine and minoxidil are available in a generic formulation. This class was last reviewed in September 2008.

Table 1. Direct Vasodilators Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Diazoxide	suspension	Proglycem®	none
Hydralazine	injection, tablet	N/A	hydralazine
Isosorbide dinitrate and hydralazine	tablet	BiDil®	none
Minoxidil	tablet	N/A	minoxidil
Nitroprusside	injection^	Nitropress®	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
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 direct vasodilators are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of heart failure and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Direct Vasodilators

Clinical Guideline	Recommendation(s)
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure**	<u>Patients With Left Ventricular Systolic Dysfunction</u> • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral

Clinical Guideline	Recommendation(s)
Practice Guideline[13] (2010)	nitrate may be considered in such patients not tolerating ARB therapy. • Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced LVEF who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. • A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy. <u>Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF</u> • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended. <u>Managing Heart Failure in Special Populations</u> • The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. • A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with LV systolic dysfunction and NYHA class II-IV heart failure.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults[12] (2009)**	<u>Patients With Current or Prior Symptoms of Heart Failure (Stage C)</u> • The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics. • The addition of a nitrate and hydralazine is reasonable in patients with reduced left ventricular ejection fraction already on an ACE inhibitor and β-blocker and who have persistent symptoms. • The combination of a nitrate and hydralazine is reasonable in patients who are intolerant to ACE inhibitor and ARB therapy or in whom therapy with one of these agents is contraindicated. <u>Special Populations</u> • The combination of a fixed-dose of isosorbide dinitrate and hydralazine to a standard medical regimen for heart failure (including ACE inhibitors and β-blockers) is recommended in order to improve outcomes for patients self-described as African Americans, with NYHA functional class III or IV heart failure. <u>Patients With Concomitant Disorders</u> • Nitrates and β-blockers are recommended in patients with heart failure and angina.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[14]**	<u>Pharmacologic Therapy of Chronic Heart Failure</u> • The combination of hydralazine and isosorbide dinitrate is recommended in symptomatic patients with an LVEF ≤40% as an alternative to an ACE inhibitor or ARB when both of the latter are not tolerated or as add-on therapy to an ACE inhibitor if an ARB or

Clinical Guideline	Recommendation(s)
(2008)	aldosterone antagonist is not tolerated. The evidence is strongest in patients of African-American descent.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management**[19] **(2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • No specific recommendation is made concerning the direct vasodilators.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension**[17] **(2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • No specific recommendation is made concerning the direct vasodilators.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update**[18] **(2006)**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • No specific recommendation is made concerning the direct vasodilators.
National Heart, Lung, and Blood	• Thiazide diuretics should be used in most patients with uncomplicated

Clinical Guideline	Recommendation(s)
Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)**[15] **(2004)**	hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease**[22] **(2004)**	• If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • No specific recommendation is made concerning the direct vasodilators.
World Health Organization (WHO)/International Society of Hypertension (ISH): **WHO/ISH Statement on Management of Hypertension**[16] **(2003)**	• If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • No specific recommendation is made concerning the direct vasodilators.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[21] **(2003)**	• No specific recommendation is made concerning the direct vasodilators.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[20] **(2010)**	• Multiple drug therapy is generally required to achieve blood pressure goals. • No specific recommendation is made concerning the direct vasodilators.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the direct vasodilators 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 Direct Vasodilators[1-5]

Indication	Diazoxide	Hydralazine	Isosorbide Dinitrate/ Hydralazine	Minoxidil
Heart Failure				
Treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status			✔	
Hypertension				
Treatment of hypertension		✔ *		✔ †
Miscellaneous				
Treatment of hypoglycemia due to hyperinsulinism	✔ ‡			

*Alone or in combination with other antihypertensive agents.
†Because of the potential for serious adverse effects, minoxidil is only indicated for the treatment of hypertension that is symptomatic or associated with target organ damage and is not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs. Use in milder degrees of hypertension is not recommended because the benefit-risk relationship in such patients has not been defined.
‡In adults: hyperinsulinism associated with inoperable islet cell adenoma or carcinoma, or extrapancreatic malignancy. In children: hyperinsulinism associated with leucine sensitivity, islet cell hyperplasia, nesidioblastosis, extrapancreatic malignancy, islet cell adenoma, or adenomatosis. It may be used preoperatively as a temporary measure, and postoperatively, if hypoglycemia persists.

IV. Pharmacokinetics

The pharmacokinetic parameters of the direct vasodilators are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Direct Vasodilators[1-5]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Diazoxide	Not reported	90	Not reported	Renal (10-90)	20-36
Hydralazine	38-50	88-90	Liver, significant	Renal (3-14) Feces (3-12)	3-5
Isosorbide dinitrate and hydralazine	H: 10-26 I: 25	H: 88-90 I: 28	Liver, significant	Not reported	2-4
Minoxidil	90-100	Insignificant	Liver (90)	Renal (90) Feces (3)	4

H=hydralazine, I=isosorbide dinitrate

V. Drug Interactions

Significant drug interactions with the direct vasodilators are listed in Table 5.

Table 5. Significant Drug Interactions with the Direct Vasodilators[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Nitrates and nitrites	1	Phosphodiesterase type 5 inhibitors	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Diazoxide	2	Hydantoins	Serum phenytoin levels may be decreased, resulting in a possible decrease in the anticonvulsant actions of phenytoin.
Diazoxide	2	Sulfonylureas	The addition of diazoxide to the regimen of a non-insulin dependent diabetic stabilized on sulfonylurea therapy may result in hyperglycemia.
Diazoxide	2	Thiazide-type diuretics	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Hydralazine	2	β-blockers	The oral bioavailability of certain high clearance, lipophilic beta-adrenergic blockers (propranolol, metoprolol) may be increased by hydralazine. The pharmacologic effects of both drugs may be increased.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the direct vasodilators are listed in Table 6. The boxed warning for minoxidil is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Direct Vasodilators[1-5]

Adverse Events	Diazoxide	Hydralazine	Isosorbide Dinitrate/ Hydralazine	Minoxidil
Cardiovascular System				
Angina pectoris	-	✔	16	✔
Cardiovascular collapse	-	-	✔	-
Crescendo angina	-	-	✔	-
Electrocardiogram changes	-	-	-	60
Flushing	-	✔	✔	-
Heart failure	-	-	-	✔
Hypotension	✔	-	8	-
Orthostatic hypotension	-	✔	✔	-
Pallor	-	-	✔	-
Palpitations	✔	✔	4	-
Paradoxical pressor response	-	✔	✔	-
Peripheral edema	-	✔	✔	7
Pericardial effusion with tamponade	-	-	-	3
Pericarditis	-	-	-	✔

Adverse Events	Diazoxide	Hydralazine	Isosorbide Dinitrate/ Hydralazine	Minoxidil
Postural hypotension	-	-	✔	✔
Rebound hypertension	-	-	✔	-
Shock	-	-	✔	-
Syncope	-	-	✔	-
Tachycardia	✔	✔	2	✔
Vascular collapse	-	✔	✔	-
Ventricular tachycardia	-	-	4	-
Central Nervous System				
Anxiety	✔	✔	✔	-
Asthenia	-	✔	✔	-
Chills	-	✔	✔	-
Depression	-	✔	✔	-
Disorientation	-	✔	✔	-
Dizziness	✔	✔	32	-
Fever	✔	✔	✔	-
Headache	✔	✔	50	-
Insomnia	✔	-	-	-
Lightheadedness	-	-	✔	-
Malaise	✔	-	-	-
Polyneuritis	✔	-	-	-
Psychotic reaction	-	✔	✔	-
Restlessness	-	-	✔	-
Dermatological				
Alopecia	✔	-	1	-
Hirsutism	✔	-	-	-
Hypertrichosis	-	-	-	80
Pruritus	✔	✔	✔	-
Purpura	✔	-	-	-
Rash	✔	✔	✔	✔
Stevens-Johnson syndrome	-	-	-	✔
Urticaria	-	✔	✔	-
Endocrine and Metabolic				
Breast lump enlargement	✔	-	-	-
Breast tenderness	✔	-	-	✔
Diabetic ketoacidosis	✔	-	-	-
Fluid and electrolyte imbalance	-	-	-	✔
Fluid retention	✔	-	-	-
Galactorrhea	✔	-	-	-
Gout	✔	-	-	-
Hyperglycemia	✔	-	4	-
Hyperlipidemia	-	-	3	-
Hyperosmolar nonketotic coma	✔	-	-	-
Pancreatitis	✔	-	-	-
Sodium retention	✔	-	-	-
Gastrointestinal				
Abdominal pain	✔	-	-	-
Anorexia	✔	✔	✔	-
Bowel incontinence	-	-	✔	-
Constipation	-	✔	✔	-
Diarrhea	✔	✔	✔	-
Ileus	✔	-	-	-
Nausea	✔	✔	10	✔
Pancreatic necrosis	✔	-	-	-

Adverse Events	Diazoxide	Hydralazine	Isosorbide Dinitrate/ Hydralazine	Minoxidil
Paralytic ileus	-	✔	✔	-
Taste loss (transient)	✔	-	-	-
Vomiting	✔	✔	4	✔
Weight gain	-	-	-	✔
Xerostomia	-	-	✔	-
Genitourinary				
Albuminuria	✔	-	-	-
Azotemia	✔	-	-	-
Blood urea nitrogen increased	-	-	-	✔
Creatine clearance decreased	✔	-	-	-
Dysuria	-	✔	✔	-
Glucosuria	✔	-	-	-
Hematuria	✔	-	-	-
Impotence	-	✔	✔	-
Nephrotic syndrome	✔	-	-	-
Serum creatine increased	-	-	-	✔
Uric acid increased	✔	-	-	-
Urinary output decreased	✔	-	-	-
Urinary incontinence	-	-	✔	-
Hematological				
Agranulocytosis	-	✔	✔	-
Bleeding	✔	-	-	-
Eosinophilia	✔	✔	✔	-
Erythrocyte count reduced	-	✔	✔	✔
Hematocrit decreased	✔	-	-	✔
Hemoglobin decreased	✔	✔	✔	✔
Hemolytic anemia	-	✔	✔	-
Leukopenia	-	✔	✔	✔
Methemoglobinemia	-	-	✔	-
Neutropenia	✔	-	-	-
Thrombocytopenia	✔	✔	✔	✔
Hepatic				
Alkaline phosphatase increased	✔	-	-	✔
ALT increased	✔	-	-	-
Cholecystitis	-	-	1	-
Musculoskeletal				
Arthralgia	-	-	1	-
Muscle cramps	-	✔	✔	-
Myalgia	-	-	1	-
Paresthesia	-	-	4	-
Peripheral neuritis	-	✔	✔	-
Rheumatoid arthritis	-	✔	✔	-
Tendon disorder	-	-	1	-
Tremor	-	✔	✔	-
Weakness	✔	✔	14	-
Ocular				
Blurred vision	✔	-	✔	-
Cataracts (transient)	✔	-	-	-
Diplopia	✔	-	-	-
Conjunctivitis	-	✔	✔	-
Lacrimation	✔	✔	✔	-
Ring scotoma	✔	-	-	-
Subconjunctival hemorrhage	✔	-	-	-

Adverse Events	Diazoxide	Hydralazine	Isosorbide Dinitrate/ Hydralazine	Minoxidil
Respiratory				
Bronchitis	-	-	8	-
Dyspnea	-	✔	✔	-
Nasal congestion	-	✔	✔	-
Pulmonary edema	-	-	-	✔
Rhinitis	-	-	4	-
Sinusitis	-	-	4	-
Other				
Abnormal facial features	✔	-	-	-
Allergic reactions	-	-	1	-
Angioedema	-	-	1	-
Diaphoresis	-	✔	1	-
Drug-induced lupus-like syndrome	-	✔	✔	-
IgG decreased	✔	-	-	-
Lymphadenopathy	✔	-	-	-

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Minoxidil[1]

WARNING
Minoxidil may produce serious adverse effects. It can cause pericardial effusion, occasionally progressing to tamponade, and it can exacerbate angina pectoris. Reserve for hypertensive patients who do not respond adequately to maximum therapeutic doses of a diuretic and 2 other antihypertensive agents. In experimental animals, minoxidil caused several kinds of myocardial lesions and other adverse cardiac effects. Administer under close supervision, usually concomitantly with a beta -adrenergic blocking agent, to prevent tachycardia and increased myocardial workload. Usually, it must be given with a diuretic, frequently one acting in the ascending limb of the loop of Henle to prevent serious fluid accumulation. When first administering minoxidil, hospitalize and monitor patients with malignant hypertension and those already receiving guanethidine to avoid too rapid or large orthostatic decreases in blood pressure.

VII. Dosing and Administration

The usual dosing regimens for the direct vasodilators are listed in Table 8.

Table 8. Usual Dosing Regimens for the Direct Vasodilators[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Diazoxide	Hypoglycemia: Initial: 3 mg/kg daily, divided into 3 equal doses administered every 8 hours; maintenance: 3 to 8 mg/kg divided into 2 or 3 equal doses administered every 8 to 12 hours	Hypoglycemia: Children: Initial: 3 mg/kg daily, divided into 3 equal doses administered every 8 hours; maintenance: 3 to 8 mg/kg divided into 2 or 3 equal doses administered every 8 to 12 hours Infants and newborns: Initial, 10 mg/kg daily in 3 equal doses administered every 8 hours; maintenance: 8 to 15 mg/kg daily divided into 2 or 3 equal doses every 8 to 12 hours	Suspension: 50 mg/ml
Hydralazine	Hypertension: Initial: 10 mg four times daily for the first 2 to 4 days, then 25 mg four times daily for the balance of the first week. For the second and subsequent weeks, increase dosage to 50 mg four times daily. For maintenance, adjust dosage to the lowest effective levels	Hypertension: Safety and effectiveness in pediatric patients have not been established in controlled clinical trials, although there is experience with the use of hydralazine in pediatric patients. Initial: 0.75 mg/kg daily administered in four divided doses. Dosage may be increased gradually over the next 3 to 4 weeks to a maximum of 7.5 mg/kg or 200 mg daily.	Injection: 20 mg/ml Tablet: 10 mg 25 mg 50 mg 100 mg
Isosorbide dinitrate and hydralazine	Heart Failure: Initial: 1 tablet 3 times daily; maximum: 2 tablets 3 times daily	The safety and effectiveness have not been established in children.	Tablet: 20 mg-37.5 mg
Minoxidil	Hypertension: Initial: 5 mg daily, increase gradually every 3 days; maintenance: 10 to 40 mg daily in single or divided doses; maximum: 100 mg daily	Hypertension: Initial: 0.2 mg/kg daily; maintenance: 0.25 to 1 mg/kg daily; maximum: 50 mg daily	Tablet: 2.5 mg 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the direct vasodilators are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Direct Vasodilators

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Heart Failure				
Unverferth et al.[27] (1983) Hydralazine 225 mg/day vs ISDN 160 mg/day vs hydralazine and ISDN (individual agents) vs placebo	DB, PC, RCT Patients with idiopathic dilated cardiomyopathy were evaluated to determine the hemodynamic and morphologic effects of vasodilator therapy	N=49 3 months	Primary: Echocardiographic percent change of left ventricular diameter, the systolic time intervals ratio of PEP/LVET, the pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and SVR	Primary: For the % change in left ventricular diameter and PEP/LVET, a significant improvement with hydralazine and combination therapy (P<0.05) was seen compared to ISDN alone or placebo. Significant decrease with ISDN and combination therapy vs placebo or hydralazine alone (P<0.05) was seen for pulmonary capillary wedge pressure, mean pulmonary artery pressure, and the pulmonary vascular resistance. Hydralazine resulted in a decrease in SVR and increase in cardiac index from 2.5±0.4 to 3.1±0.4 L/min/m^2 vs placebo or ISDN alone (P<0.05). Combination therapy resulted in a decrease in SVR and cardiac index increased from 2.3±0.4 to 3.1±0.4 L/min/m^2 (P<0.01). There was no improvement in SVR or cardiac index with ISDN alone or with placebo. Myocardial cell diameter decreased from 25.4±3.1 microns at baseline to 23.1±3.8 microns with hydralazine (P<0.05). Combination therapy decreased its cell diameter from 23.9±3.7 to 22.2±2.2 microns (P<0.05). There was no change in the myocardial cell diameter seen in patients treated with ISDN alone or with placebo.
Taylor[28] (2005) A-HeFT Hydralazine 112.5	DB, MC, PC, RCT African American patients with moderate-to-severe symptomatic heart	N=1,050 6-18 months	Primary: Composite score (all-cause mortality, first hospitalization for heart failure, and	Primary: Mortality in the fixed-dose hydralazine-ISDN group was 6.2% compared with 10.2% in the placebo group (P=0.02). Survival was increased by 43% in the active treatment arm (HR, 0.57; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day with ISDN 60 mg/day in 3 divided doses titrated up to hydralazine 225 mg/day with ISDN 120 mg/day in 3 divided doses (fixed-dose combination) vs placebo	failure, classified NYHA class III-IV heart failure with dilated ventricles and low ejection fractions		quality of life at 6 months as measured by the Minnesota Living with Heart Failure questionnaire)	The composite score and all individual components of the composite score were significantly and positively impacted by treatment with hydralazine-ISDN (primary composite score P=0.01, death from any cause P=0.02, first hospitalization for heart failure P=0.001, change in quality of life score at 6 months P=0.02). The study was prematurely terminated in as a result of the significantly improved survival in the hydralazine-ISDN group.
Taylor et al.[29] (2004) A-HeFT Hydralazine 37.5 mg plus ISDN 20 mg TID increased to hydralazine 75 mg plus ISDN 40 mg TID (fixed-dose combination) 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, and 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 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 hydralazine plus ISDN when compared to placebo (–5.6±20.6 vs –2.7±21.2; P=0.02).
Taylor et al.[30] (2007) A-HeFT	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of	N=1,050 Mean duration of follow-up was 18 months	Primary: Event-free survival (death or first hospitalization for heart failure heart	Primary: In the treatment group event-free survival (death or first hospitalization for heart failure) was significantly improved compared with placebo (HR, 0.63; 95% CI, 0.49 to 0.81; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hydralazine 37.5 mg plus ISDN 20 mg TID increased to hydralazine 75 mg plus ISDN 40 mg TID (fixed-dose combination) vs placebo	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		failure), time to first hospitalization Secondary: Individual components of the primary composite score	The time to first hospitalization for heart failure was also significantly reduced (HR, 0.61; 95% CI, 0.46 to 0.80; P<0.001). Secondary: A consistent beneficial effect was seen in the treatment sub groups (age, sex, baseline blood pressure, history of chronic renal insufficiency, presence of diabetes, cause of heart failure, and baseline medication use) on primary composite score and event-free survival.
Yancy et al.[31] (2007) A-HeFT Hydralazine 37.5 mg plus ISDN 20 mg TID increased to hydralazine 75 mg plus ISDN 40 mg TID (fixed-dose combination) 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 18 months	Primary: Compliance with study drug, safety, tolerability Secondary: Change in NYHA association class, death, hospitalization for heart failure	Primary: Compliance in the treatment group averaged 87%±25%, with no significant difference when compared to placebo. There were no significant differences in adverse events between treatment groups. Secondary: No significant difference was seen in hospitalizations from heart failure according to randomization. The greatest improvement in heart failure symptoms occurred in NYHA class III (at baseline) compared to other classes (P<0.001). Overall most patients were unchanged with 24% showing improved NYHA class and 9% showing a worsening.
Cohn et al.[32] (1986) V-HeFT I Hydralazine 300 mg daily plus ISDN 160 mg daily (individual agents, concurrent	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 hydralazine plus ISDN group compared to placebo (P<0.028). Cumulative mortality rates of 25.6% and 36.2% were observed in the hydralazine plus ISDN 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:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy) vs prazosin 20 mg daily vs placebo				A significant increase in the left ventricular ejection fraction was reported at 8 weeks and 1 year in the hydralazine plus ISDN treatment group, but not in either the prazosin or placebo groups.
Cohn et al.[33] (1991) V-HeFT II Hydralazine 300 mg/day plus ISDN 160 mg/day (individual agents, concurrent therapy) vs enalapril 20 mg/day	DB, RCT Men receiving digoxin and diuretic therapy for heart failure	N=804 2 years	Primary: Mortality, body oxygen consumption at peak exercise, left ventricular ejection fraction	Primary: Mortality after two years was significantly lower in the enalapril arm (18%) than in the hydralazine-ISDN arm (25%) (P=0.016). Body oxygen consumption at peak exercise was increased only by hydralazine-ISDN treatment (P<0.05). Left ventricular ejection fraction, which increased with both regimens during the 2 years after randomization, increased more (P<0.05) during the first 13 weeks in the hydralazine-ISDN group.
Mullens et al.[34] (2009) Isosorbide dinitrate and hydralazine (I/H) added to an ACE inhibitor or angiotensin receptor blockers	PRO Patients ≥18 years of age with advanced decompensate heart failure (ADHF) with a cardiac index <2.2 L/min/m^2 who were admitted to the	N=239 Mean 26.3 months	Primary: All-cause mortality, cardiac transplantation, and first readmission for HF after index hospitalization discharge	Primary: Patients receiving I/H had lower all-cause mortality (34% vs 41%; OR, 0.65; 95% CI, 0.43 to 0.99, P=0.04) and lower all-cause mortality/HF rehospitalization (70% vs 85%; OR, 0.72; 95% CI, 0.54 to 0.97; P=0.03) compared with the control group. There was no difference in overall cardiac transplantation or HF rehospitalization rates among the treatment groups. The improved outcomes in the I/H group was independent of race; however, there was a trend toward improved outcomes in African-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ACE inhibitor or angiotensin receptor blockers Titration of oral drugs was aimed to wean off parental therapy and based on maintaining a target mean arterial pressure of 65 to 70 mm Hg and/or systolic blood pressure >85 mm Hg	hospital for intensive medical therapy			Americans (all-cause mortality for whites in the I/H group, OR 0.66; 95% CI, 0.4 to 0.98; P=0.05; all-cause mortality for African-Americans in the I/H group, OR 0.44; 95% CI, 0.23 to 0.85; P=0.01).
Hypertension				
Johnson et al.[23] (1983) Minoxidil 5 to 40 mg/day as add-on therapy vs hydralazine 25 to 200 mg/day as add-on therapy	DB, RCT Patients with normal renal function receiving HCTZ or propranolol (doses unknown) with DBP >95 mm Hg	N=36 28 weeks	Primary: Percentage of patients with DBP <90 mm Hg at weeks 4 and 28	Primary: There were greater response rates (DBP <90 mm Hg) with minoxidil (69%) vs hydralazine (35%) at week 4. At week 28, there were greater response rates (DBP <90 mm Hg) with minoxidil (55%) vs hydralazine (40%).
Bevan et al.[24] (1993) Captopril (unknown dose) vs	DB, PC, RCT Patients with inadequately controlled hypertension, despite treatment	N=160 12 weeks	Primary: Comparative antihypertensive, biochemical, and adverse effects	Primary: Mean supine blood pressure changes: captopril 13.4/10.3 mm Hg, hydralazine 15.0/10.0 mm Hg, and nifedipine 16.8/8.1 mm Hg (differences not significant). Erect blood pressure changes were similar; target blood pressure (<140/95 mm Hg) was achieved in 33% with captopril, 29% with hydralazine, 17%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydralazine (unknown dose) vs nifedipine (unknown dose) vs placebo	with atenolol 100 mg/day and bendrofluazide* 5 mg/day			with nifedipine, and 10% with placebo. Compared with other agents, captopril increased serum potassium (value not reported; P=0.01). Mean changes in serum cholesterol: captopril -0.2 mmol/L, hydralazine -0.8 mmol/L, nifedipine -0.2 mmol/L, and placebo +0.2 mmol/L (P<0.001). Side effects did not differ significantly between the groups. Withdrawal rates: captopril 15%, hydralazine 24%, nifedipine 22%, and placebo 3% (P=0.04).
Julien et al.[25] (1990) Captopril 150 to 300 mg/day vs minoxidil 7.5 to 30 mg/day	DB, PG, RCT Male patients with left ventricular hypertrophy and essential hypertension with DBP >95 mm Hg who were taking metoprolol 200 mg/day and furosemide 80 mg/day	N=34 6 months	Primary: Blood pressure changes and left ventricular hypertrophy changes as seen on electrocardiogram	Primary: Blood pressure decreased significantly in both groups; captopril (163/102 to 135/89 mm Hg) and minoxidil (160/99 to 137/87 mm Hg; P<0.001). Electrocardiogram criteria for left ventricular hypertrophy improved with captopril only with a decrease in intraventricular septum, posterior wall, and left ventricular mass (17.4 to 15.9 mm; P<0.05, 14.5 to 13.4 mm; P<0.05 and 236 to 198 g/m^2; P<0.001, respectively). No changes on electrocardiogram criteria with minoxidil.
McAreavey et al.[26] (1984) Hydralazine 12.5 mg QD up to 100 mg BID vs labetalol 200 mg QD up to 1,600 mg BID	DB, PG, RCT Patients with inadequately controlled hypertension while taking atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=238 6 months	Primary: Comparative safety and efficacy, target blood pressure <140/95 mm Hg	Primary: Target blood pressure goal was reached in 25% of hydralazine group, 23% with minoxidil, 19% with prazosin, 17% with methyldopa, and 0% with placebo. Labetalol had the highest withdrawal rate 78% (P<0.05) vs other groups. Minoxidil had the second highest withdrawal rate 57% (P<0.05) due to fluid retention. There were no significant differences in withdrawal rates among the other groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs methyldopa 125 mg QD up to 1,000 mg BID vs prazosin 0.5 mg QD up to 10 mg BID vs placebo Minoxidil as add-on therapy was given to men only.				

*Synonym for bendroflumethiazide.
Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: AC=active-controlled, DB=double-blind, HR=hazard ratio, MC=multicenter, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, HF=heart failure, ISDN=isosorbide dinitrate, LVEF=left ventricular ejection fraction, LVET=left ventricular ejection time, NYHA-New York Heart Association, PEP=pre-ejection period, SVR=systemic vascular resistance

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 10. Relative Cost of the Direct Vasodilators

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Diazoxide	suspension	Proglycem®	$$$$$	N/A
Hydralazine	injection, tablet	N/A	N/A	$
Isosorbide dinitrate and hydralazine	tablet	BiDil®	$$$$	N/A
Minoxidil	tablet	N/A	N/A	$

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

X. Conclusions

Diazoxide is a non-diuretic benzothiadiazine derivative taken orally for the management of symptomatic hypoglycemia.[4] It increases blood glucose levels by inhibiting the release of insulin from the pancreas, as well as by an extrapancreatic effect. The hyperglycemic effect begins within an hour and generally last no more than 8 hours. The oral preparation does not demonstrate the same effects on blood pressure as the other direct vasodilators. Diazoxide is considered a first-line treatment option for hypoglycemia due to hyperinsulinism.[6,8] It is not available in a generic formulation.

Hydralazine and minoxidil are approved for the treatment of hypertension, and both agents are available in a generic formulation.[1-3] There are several national and international organizations that have published guidelines on the treatment of hypertension; however, they do not provide recommendations on the use of the oral direct vasodilators.[15-22] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[15-16,18,22] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[17,19] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[17,19] All of the available guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use. Most patients will need more than one antihypertensive agent to achieve blood pressure goals. Clinical studies have demonstrated that hydralazine and minoxidil are effective for the treatment of hypertension when added to existing therapy in patients whose blood pressure is inadequately controlled.[23-26] There are limited head-to-head trials comparing the direct vasodilators. These agents are associated with several potentially severe adverse effects, which limits their use in the treatment of hypertension.

Hydralazine and isosorbide dinitrate (administered as single entity products) have been used off-label to treat heart failure for many years. The combination of these agents has been shown to reduce mortality compared to placebo in patients receiving standard therapy with digoxin and diuretics.[32] However, when hydralazine and isosorbide dinitrate were directly compared to an ACE inhibitor, mortality was significantly lower in the ACE inhibitor group.[33] Guidelines currently recommend the use of hydralazine and an oral nitrate in patients who do not tolerate an ACE inhibitor or angiotensin II receptor antagonist.[12-14] The fixed-dose combination of isosorbide dinitrate and hydralazine is FDA-approved for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients.[5] In the A-HeFT trial, the use of this combination product improved mortality, prolonged time to hospitalization for heart failure, and improved functional status compared to placebo.[5,28-31] The patients in this trial were also receiving standard heart failure therapy prior to enrollment (ACE inhibitors, angiotensin II receptor antagonists, β-blockers, diuretics, digoxin, spironolactone). The Heart Failure Society of America and the American College of Cardiology Foundation/American Heart Association recommend the use of the combination of isosorbide dinitrate and hydralazine in African American patients with NYHA functional class III or IV heart failure who are on a standard regimen including an ACE inhibitor (or angiotensin II receptor antagonist) and a β-blocker.[12-13] Both hydralazine and isosorbide dinitrate are available generically; however, generic hydralazine is not available in a strength equivalent to the fixed-dose combination product.

Therefore, all brand direct vasodilators 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. The fixed-dose combination of isosorbide dinitrate and hydralazine (BiDil®) should be available through the medical justification portion of the prior authorization process as an adjunct to standard heart failure therapy in self-identified black patients. Due to its limited FDA-approved indications, diazoxide (Proglycem®) should be managed through the existing medical justification portion of the prior authorization process.

XI. Recommendations

No brand direct vasodilator 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 Peripheral Adrenergic Inhibitors
AHFS Class 240832
November 10, 2010

I. Overview

Reserpine is approved for the treatment of mild hypertension as monotherapy, as well as adjunctive therapy in more severe forms of hypertension.[1-4] Additionally, reserpine is approved for the treatment of symptoms in agitated psychotic states (e.g., schizophrenia), primarily in those individuals unable to tolerate phenothiazine derivatives or in those who also require antihypertensive medication.[1-4] Reserpine depletes norepinephrine and serotonin stores both centrally and in the peripheral adrenergic nerve endings. It also blocks the transport of norepinephrine into its storage granules. Reserpine depletes catecholamines from the brain and myocardium and increases vagal tone, which may lead to decreased cardiac output, depression and sedation.[5-6]

The peripheral adrenergic inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Reserpine is available in a generic formulation. This class was last reviewed in September 2008.

Table 1. Peripheral Adrenergic Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Reserpine	tablet	N/A	reserpine

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 peripheral adrenergic inhibitors are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Peripheral Adrenergic Inhibitors

Clinical Guideline	Recommendation(s)
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management[11] (2009)**	• No specific recommendation is made concerning reserpine.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[9] (2007)**	• No specific recommendation is made concerning reserpine.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[10] (2006)**	• No specific recommendation is made concerning reserpine.

Clinical Guideline	Recommendation(s)
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, And Treatment of High Blood Pressure (JNC 7)[7] (2004)**	• No specific recommendation is made concerning reserpine.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[14] (2004)**	• No specific recommendation is made concerning reserpine.
World Health Organization (WHO)/International Society of Hypertension (ISH): **WHO/ISH Statement on Management of Hypertension[8] (2003)**	• No specific recommendation is made concerning reserpine.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans[13] (2003)**	• No specific recommendation is made concerning reserpine.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[12] (2010)**	• No specific recommendation is made concerning reserpine.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the peripheral adrenergic 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 Peripheral Adrenergic Inhibitors[1-4]

Indication	Reserpine
Hypertension	
Treatment of mild essential hypertension	✔ *
Miscellaneous	
Treatment of symptoms in agitated psychotic states (e.g., schizophrenia), primarily in those individuals unable to tolerate phenothiazine derivatives or in those who also require antihypertensive medication	✔

*Also useful as adjunctive therapy with other antihypertensive agents in the more severe forms of hypertension.

IV. Pharmacokinetics

The pharmacokinetic parameters of the peripheral adrenergic inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Peripheral Adrenergic Inhibitors[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Reserpine	30-40	96	Liver (>90)	Renal (12) Feces (60)	50-100

V. Drug Interactions

Significant drug interactions with the peripheral adrenergic inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Peripheral Adrenergic Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Reserpine	2	Iobenguane	Depletion of norepinephrine storage vesicles by reserpine may result in decreased retention of the structurally similar iobenguane, possibly resulting in false-negative iobenguane imaging results.
Reserpine	2	Tetrabenazine	Both reserpine and tetrabenazine inhibit human vesicular monoamine transporter type-2 (VMAT2). Coadministration of tetrabenazine with reserpine may deplete serotonin and norepinephrine in the central nervous system. Pharmacologic effects of tetrabenazine may be increased by reserpine.

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

VI. Adverse Drug Events

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

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

Adverse Events	Reserpine
Cardiovascular	
Angina	✔
Arrhythmia	✔
Bradycardia	✔
Edema	✔
Hypotension	✔
Premature ventricular contractions	✔
Syncope	✔
Central Nervous System	
Depression	✔
Dizziness	✔
Drowsiness	✔

Adverse Events	Reserpine
Dull sensorium	✔
Fatigue	✔
Headache	✔
Nervousness	✔
Nightmares	✔
Paradoxical anxiety	✔
Parkinsonism	✔
Dermatological	
Flushing	✔
Pruritus	✔
Purpura	✔
Rash	✔
Endocrine and Metabolic	
Gynecomastia	✔
Weight gain	✔
Gastrointestinal	
Anorexia	✔
Diarrhea	✔
Dry mouth	✔
Gastric acid secretion increased	✔
Nausea	✔
Salivation increased	✔
Vomiting	✔
Genitourinary	
Impotence	✔
Libido decreased	✔
Hematologic	
Thrombocytopenia purpura	✔
Musculoskeletal	
Muscle ache	✔
Respiratory	
Dyspnea	✔
Epistaxis	✔
Nasal congestion	✔
Other	
Blurred vision	✔
Optic atrophy	✔

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the peripheral adrenergic inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Peripheral Adrenergic Inhibitors[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Reserpine	Hypertension: Initial 0.5 mg/day for 1 to 2 weeks; maintenance 0.1 to 0.25 mg/day Psychiatric Disorders: Initial 0.5 mg/day; titrate as necessary	Not recommended for use in children. If it is to be used in treating a child, the usual recommended starting dose is 20 mcg/kg daily; maximum 0.25 mg (daily) dose	Tablet: 0.1 mg 0.25 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the peripheral adrenergic inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Peripheral Adrenergic Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypertension				
Finnerty et al.[15] (1980) Chlorthalidone 50 mg plus reserpine 0.25 mg vs HCTZ 50 mg plus reserpine 0.125 mg	CT, DB Patients with essential hypertension unresponsive to diet control and diuretic therapy	N=57 6 weeks	Primary: The change in mean DBP from baseline Secondary: Incidence of frequent or severe side effects	Primary: The chlorthalidone plus reserpine group had a mean decrease in DBP of 17.0 mm Hg at study endpoint compared with a mean decrease of 18.6 mm Hg in the HCTZ plus reserpine group. At study completion both treatment groups achieved diastolic control of at least 5 mm Hg below the targeted diastolic goal of 90 mm Hg. Secondary: There were no reports of frequent or severe side effects in either treatment group.
Finnerty et al.[16] (1979) Hydro-flumethiazide 50 mg or 100 mg QD plus reserpine 0.125 mg to 0.25 mg QD vs hydro-flumethiazide 50 mg or 100 mg QD plus methyldopa 500 mg to 2,000 mg QD vs	CT, SB Patients with hypertension unresponsive to hydroflumethiazide alone	N=59 9 weeks	Primary: Percentage of patients achieving a DBP below 90 mm Hg	Primary: At study endpoint, the DBP below 90 mm Hg was achieved in all 20 patients (100%) treated with hydroflumethiazide plus reserpine, 13 of the 19 patients (68.4%) treated with hydroflumethiazide plus methyldopa, and in 16 of the 20 patients (80%) treated with hydroflumethiazide plus propranolol.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hydro-flumethiazide 50 mg or 100 mg QD plus propranolol 80 mg to 320 mg QD				
Kostis et al.[17] (1995) SHEP Chlorthalidone 12.5 mg QD vs placebo If goal SBP was not achieved, the dosage of chlorthalidone was increased to 25 mg QD or matching placebo. If goal SBP still not reached, atenolol 25 mg QD or matching placebo was added. Reserpine 0.05 to 0.1 mg QD or matching placebo was used if atenolol was contraindicated or	DB, MC, PC, RCT Persons aged ≥60 years with isolated systolic hypertension defined as a SBP 160 to 219 mm Hg and a DBP <90 mm Hg	N=4,736 4.5 years (mean)	Primary: Total mortality, fatal and nonfatal stroke combined, coronary heart disease (fatal and nonfatal myocardial infarction, sudden death, rapid death), cardiovascular disease (also including coronary heart disease and stroke)	Primary: There were 2,365 patients randomized to active treatment and 2,371 patients randomized to placebo, with a mean follow-up of 4.5 years. Of the 2,365 patients on active treatment, 193 (8%) received reserpine for an average of 1.7 years (at risk for 2.7 person-years after first exposure); of the 193 patients, 117 (61%) received reserpine for >1 year. Conversely, 757 (32%) were on atenolol with an average exposure of 2 years (at risk for 2,311 person years after first exposure). Incident stroke was observed in 103 patients in the active group and 159 patients in the placebo (RR, 0.64; 95% CI, 0.50 to 0.82). Nonfatal myocardial infarction or coronary heart disease deaths in the active group occurred in 104 patients and 141 in the placebo group (RR, 0.73; 95% CI, 0.57 to 0.94), while 289 cardiovascular disease events occurred in the active group compared with 414 in the placebo group (RR, 0.68; 95% CI, 0.58 to 0.79). After adjustments for multiple baseline covariates, the relative risks in the reserpine group were 0.65 (95% CI, 0.26 to 1.59) for death, 0.27 (95% CI, 0.04 to 2.26) for stroke, 0.93 (95% CI, 0.29 to 2.96) for coronary heart disease events, and 0.55 (95% CI, 0.20, 1.49) for cardiovascular disease events. The relative risks in the atenolol group after adjustments for multiple baseline covariates were 0.84 (95% CI, 0.54 to 1.30) for death, 1.34 (95% CI, 0.80 to 2.28) for stroke, 1.04 (95% CI, 0.58 to 1.87) for coronary heart disease events and 1.07 (95 % CI, 0.71, 1.61) for cardiovascular disease events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
if intolerable side effects with atenolol occurred.				
Krönig et al.[18] (1997) Reserpine 0.1 to 0.2 mg QD plus clopamid* 5 to 10 mg QD vs reserpine 0.1 to 0.2 mg QD vs clopamide 5 to 10 mg QD vs nitrendipine* 20 to 40 mg QD	AC, MC, PG, RCT German patients ≥18 years with mild to moderate hypertension and a DBP of 100 to 114 mm Hg at rest	N=273 12 weeks	Primary: The change in sitting DBP and SBP from baseline to weeks 6 and 12, and the number of patients achieving the goal DBP and SBP Secondary: Changes in heart rate, incidence of adverse events, and laboratory safety parameter measurements	Primary: The reduction in DBP was similar in the reserpine, clopamide, and nitrendipine groups at week six (–11.7, –11.9, and –12.3 mm Hg), but was greater in the combination group (–17.1 mm Hg). The difference was statistically significant when the combination group was compared with each of the monotherapy groups (P<0.001) and the nitrendipine group (P=0.002). At week 12, the change in DBP compared to baseline was –12.2, –13.4, and –15.3 mm Hg in the reserpine, clopamide, and nitrendipine groups, compared to –18.1 mm Hg in the combination group. The number of patients in the combination group achieving normal DBP readings, defined as a trough <90 mm Hg) by week 6 was 55.2% compared with 39.7%, 36.2%, and 33.3% in the reserpine, clopamide, and nitrendipine groups, (P=0.11). Patients not achieving goal DBP at week 6 subsequently had their medication doses increased, which resulted in achievement of DBP goal in 65.7% of patients in the combination group, and 35.3%, 39.1%, and 44.9% in the reserpine, clopamide, and nitrendipine groups, (P<0.0001). The reduction in SBP at week 6 in the combination group (–23.0 mm Hg) was greater compared to the reserpine, clopamide, and nitrendipine groups (–14.0, –13.6, and –11.6 mm Hg); P <0.001), resulting in rates of 62.7%, 45.6%, 40.6%, and 30.4% of patients achieving the goal SBP at week 6. Dose titration in those not achieving goal SBP by week 6 resulted in further SBP reductions in all groups except for the reserpine monotherapy group; and normalization was achieved at 12 weeks in 76.1% of the combination group compared with 44.1%, 46.4%, and 39.1% of the reserpine, clopamide, and nitrendipine groups compared to baseline. Secondary: Mean baseline heart rates were 74.9, 75.6, 75.2, and 73.8 beats per minute for the combination, reserpine, clopamide, and nitrendipine groups. Heart rate measurements remained constant in the clopamide and nitrendipine groups and fell in the reserpine and reserpine-clopamide groups by 5.6 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				5.3 beats per minute, by week 12. The percentages of patients with one or more adverse events experienced by week 12 were almost the same in the combination group versus the reserpine and clopamide monotherapy groups (27% vs 28% and 29%), whereas the incidence of adverse events was 48% in the nitrendipine group (P=0.01). The numbers of patients withdrawing from the study due to adverse experiences were 2 (3%) each in the reserpine-clopamide group and reserpine groups, 5 (7%) in the clopamide group, and 9 (13%) in the nitrendipine group. Two serious events were investigator-determined as possibly drug related, resulting in study discontinuation; one in the clopamide group at 6 weeks (uterine bleeding) and one in the nitrendipine group at 12 weeks (tarry stools). The percentage of patients achieving goal DBP without an adverse events was 49% in the combination group, compared with 19%, 20%, and 12% in the reserpine, clopamide, and nitrendipine groups (P<0.0001). Body weight and electrocardiographic measurements did not change significantly in any group at 12 weeks compared to baseline.
Manyemba et al.[19] (1997) HCTZ 25 mg QD plus reserpine 0.25 mg QD vs HCTZ 25 mg QD plus nifedipine SR 20 mg BID	OL, RCT, XO African American patients aged 21-65 years with hypertension (blood pressure >140/95 mm Hg) after 4 weeks of daily HCTZ therapy	N=32 10 weeks	Primary: The change in blood pressure from baseline to the end of each 4-week treatment period	Primary: Reserpine reduced SBP by 15.9 mm Hg (95% CI, 8.4 to 23.4) and DBP by 11.1 mm Hg (95% CI, 7.5 to 14.6). Nifedipine SR reduced SBP by 18.9 mm Hg (95% CI, 12.1 to 25.7) and DBP by 9.6 mm Hg (95% CI, 7.2 to 12.0). There was no significant difference between the two groups.
Materson et al.[20] (1990)	DB, MC, RCT Men ≥60 years with	N=690 12 months	Primary: Average reduction in SBP, DBP, the	Primary: A total of 269 patients were uncontrolled with HCTZ therapy alone and were randomized to receive hydralazine (n=68), methyldopa (n=71),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 25 to 100 mg QD plus hydralazine 25, 50, or 100 mg BID vs HCTZ 25 to 100 mg QD plus methyldopa 250, 500, 1,000 mg BID vs HCTZ 25 to 100 mg QD plus metoprolol 50, 100, or 200 mg BID vs HCTZ 25 to 100 mg QD plus reserpine 0.05, 0.10, or 0.25 mg QD	hypertension not currently receiving antihypertensive therapy with a DBP 90-114 mm Hg and a SBP <240 mm Hg; or a DBP <100 mm Hg and a SBP <240 mm Hg if currently taking antihypertensive therapy and the blood pressure criteria was met after at least 2 weeks without medication		number of patients achieving the goal blood pressure and the average change in heart rate Secondary: Rates of drug intolerances and incidence of adverse effects	metoprolol (n=65), or reserpine (n=65). A total of 213 of the 269 patients achieved goal blood pressure with the addition of one of four therapies was added to HCTZ and entered the 6 month maintenance phase; 186 patients completed the maintenance phase. Across all 4 add-on therapies, there was an additional average reduction in blood pressure of 13.1/10.6 mm Hg. The average reduction in SBP (mm Hg)±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: –11.5±10.1 (P<0.001), –15.0±13.7 (P<0.001), –13.0±15.4 (P<0.001), and –12.7±11.5 (P<0.001), respectively. There was no statistically significant difference in SBP reductions among the different groups (P=0.43). The average reduction in DBP (mm Hg)±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: –11.3±5.9 (P<0.001), –10.6±6.3 (P<0.001), –10.6±6.7 (P<0.001), and –9.8±6.3 (P<0.001), respectively. There was no statistically significant difference in DBP reductions among the different groups (P=0.59). The average change in heart rate (beats per minute) ±SD from baseline to endpoint for hydralazine, methyldopa, metoprolol, and reserpine add-on therapies was: 1.4±10.5 (P=NS), –1.6±9.3 (P=NS), 15.9±11.9 (P<0.05), and -7.9±10.7 (P<0.05), respectively. There was a statistically significant difference in change in heart rate among the different groups (P<0.001). The percentage of patients achieving the goal blood pressure at endpoint in the hydralazine, methyldopa, metoprolol, and reserpine groups was: 85.3%, 81.7%, 76.9%, and 72.3%, respectively (P=0.28). Secondary: Drug intolerance, defined as adverse effects prompting dose reduction or discontinuation, was present in 23.3% of those not achieving goal blood pressure compared with 2.8% of those achieving the goal blood pressure (P<0.001). This was statistically significant in the hydralazine, methyldopa, and metoprolol groups, but not the reserpine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were 27 (10%) study terminations due to adverse drug events: hydralazine (n=3), methyldopa (n=8), metoprolol (n=9), and reserpine (n=7). There were 2 study terminations in the methyldopa-treated group and 1 in the reserpine group due to depression. The overall incidence of volunteered moderate or severe adverse effects, not prompting study termination was significantly greater (P<0.01) with methyldopa (31%) and hydralazine (25%) compared with reserpine (15%) or metoprolol (9%).
VA Medical Centers[21] (1982) Chlorthalidone 50 mg QD plus reserpine 0.25 mg QD vs chlorthalidone 50 mg QD plus reserpine 0.125 mg QD vs chlorthalidone 50 mg QD plus reserpine 0.05 mg QD vs chlorthalidone 25 mg QD plus reserpine 0.125 mg	DB, MC, RCT Patients with mild to moderate hypertension who did not achieve normal blood pressure with chlorthalidone therapy alone	N=329 12 weeks	Primary: Changes in DBP and SBP readings and the percentage of patients achieving control at a DBP <90 mm Hg and at least 5 mm Hg below baseline Secondary: Side effects	Primary: The reduction in blood pressure (SBP/DBP) when reserpine was added to patient's chlorthalidone therapy averaged 11.0/10.4 mm Hg with chlorthalidone 50 mg plus reserpine 0.25 mg; 9.5/9.4 mm Hg with chlorthalidone 50 mg plus reserpine 0.125 mg; 6.4/8.5 mm Hg with chlorthalidone 50 mg plus reserpine 0.05 mg; and 9.9/9.6 mm Hg with chlorthalidone 25 mg plus reserpine 0.125 mg. The percentage of patients in whom control was achieved at DBP less than 90 mm Hg and at least 5 mm Hg below baseline with either chlorthalidone alone or in with reserpine was: 65% with chlorthalidone 50 mg plus reserpine 0.25 mg; 69% with chlorthalidone 50 mg plus reserpine 0.125 mg; 58% with chlorthalidone 50 mg plus reserpine 0.05 mg; and 56% with chlorthalidone 25 mg plus reserpine 0.125 mg. Secondary: Side effects of lethargy and impotence noted by patients with the 0.05 mg dose of reserpine were one third of the reports noted with the 0.25 mg dose. The incidence of other side effects did not differ.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD				
Shamon et al.[23] (2009) Reserpine monotherapy vs placebo or no treatment	MA Patients with primary hypertension	N=237 (4 trials) 3-12 weeks	Primary: Changes in systolic and diastolic blood pressure Secondary: Changes in mean arterial blood pressure and heart rate	Primary: Three trials reported systolic blood pressure (SBP) and diastolic blood pressure (DBP) data. The pooled effect showed a significant reduction in SBP in favor of reserpine compared to placebo (WMD -7.92, 95% CI, -14.05 to -1.78). There was no significant difference in DBP between reserpine and placebo (WMD -4.15, 95%CI, -9.19 to 0.90). Secondary: Three trials reported changes in mean arterial pressure (MAP). The pooled effect showed a significant reduction in MAP with reserpine (WMD -7.10, 95% CI, -11.81 to -2.38). However, there was significant heterogeneity across trials and this effect was no longer significant when random model effect was applied. Two trials reported changes in heart rate. The pooled effect showed a significant reduction in HR with reserpine (WMD -8.82, 95% CI, -14.20 to -3.43, P=0.001). However, there was significant heterogeneity across trials and this effect was no longer significant when random model effect was applied.
Psychotic States				
Berlant et al.[22] (1986) Reserpine in combination with neuroleptics	RETRO Chronically disabled psychotic patients with symptoms refractory to lithium and neuroleptics	N=36 Duration not specified	Primary: The change in chronically persistent psychotic symptoms and functionality	Primary: There was a moderate to dramatic response rate in 50% of the 36 chronically disabled psychotic patients with the addition of reserpine to neuroleptic and lithium therapies. The observed improvement was distinct compared to the baseline pattern of chronically persistent psychotic symptoms and poor functioning. Female patients and those with schizoaffective or bipolar disorders tended to respond best to treatment.

*Agent not commercially available in the United States (U.S.).
Drug regimen abbreviations: BID=twice daily, HCTZ=hydrochlorothiazide, QD=once daily, SR=sustained release
Study abbreviations: AC=active-controlled, CI=confidence interval, CT=controlled trial, DB=double blind, MC=multicenter, OL=open label, NS=not significant, PC=placebo-controlled, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SB=single blind, WMD=weighted mean difference, XO=crossover
Miscellaneous abbreviations: DBP=diastolic blood pressure, SBP=systolic blood pressure, VA – Veterans Administration

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 Peripheral Adrenergic Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Reserpine	tablet	N/A	N/A	$

N/A=Not available

X. Conclusions

Reserpine is approved for the treatment of mild hypertension as monotherapy, as well as adjunctive therapy in more severe forms of hypertension.[1-4] Additionally, reserpine is approved for the treatment of symptoms in agitated psychotic states (e.g., schizophrenia), primarily in those individuals unable to tolerate phenothiazine derivatives or in those who also require antihypertensive medication.[1-4] Reserpine is available in a generic formulation.

There are several national and international organizations that have published guidelines on the treatment of hypertension; however, they do not address the use of reserpine.[7-14] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[7-8,10,14]According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[9,11] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[9,11] All of the available guidelines consistently recommend that the selection of an

antihypertensive agent be based on compelling indications for use. Reserpine has been shown to be effective for the treatment of hypertension when administered as monotherapy or as a second-line agent.[15-16,18-21,23] However, its use is associated with many adverse events, including depression, nasal congestion and gastrointestinal symptoms.[1-4,6]

Therefore, all brand peripheral adrenergic 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 peripheral adrenergic 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 Hypotensive Agents, Miscellaneous
AHFS Class 240892
November 10, 2010

I. Overview

Fenoldopam is the only miscellaneous hypotensive agent that is currently available. It is indicated for the in-hospital, short-term (up to 48 hours) management of severe hypertension when rapid, but quickly reversible, emergency reduction of blood pressure is clinically indicated, including malignant hypertension with deteriorating end-organ function.[1-3] Oral mecamylamine (Inversine®) was previously included in this class review; however, as of September 30, 2010, there are no longer any covered NDCs for this product.

The miscellaneous hypotensive agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. This class was last reviewed in September 2008.

Table 1. Miscellaneous Hypotensive Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fenoldopam	injection^	Corlopam®*	none

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List

II. Conclusions

There are currently no covered outpatient drugs available in the miscellaneous hypotensive agents class (AHFS Class 240892).

III. Recommendations

No brand miscellaneous hypotensive agent is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 240892 in the PDL screening process. If new outpatient miscellaneous hypotensive agents are added, it is recommended that this class be re-reviewed at that time.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alpha-Adrenergic Blocking Agents
AHFS Class 242000
November 10, 2010

I. Overview

The alpha-adrenergic blocking agents are approved for the treatment of benign prostatic hyperplasia (BPH) and hypertension.[1-6] However, the use of these agents for the treatment of hypertension is somewhat limited due to adverse events. They can cause postural hypotension, reducing the standing systolic blood pressure by more than 10 mm Hg. Syncope with sudden loss of consciousness can also occur, especially with the first few doses, rapid dose increases, or the addition of another antihypertensive agent to the treatment regimen. Unlike diuretics and beta-adrenergic blocking agents, alpha-adrenergic blocking agents do not adversely affect lipids. They have been shown to reduce total cholesterol by 3% to 5% and triglycerides by 3% to 4%, as well as increase high-density lipoprotein cholesterol.[17] The alpha-adrenergic blocking agents are more commonly used to relieve symptoms of BPH, which is characterized by an enlargement of the prostate gland. BPH is associated with lower urinary tract symptoms, such as frequent daytime urination, nocturia, a sensation of incomplete bladder emptying and a hesitant, weak, or intermittent urinary stream.

The alpha-adrenergic blocking agents competitively inhibit postsynaptic α_1-adrenergic receptors, which are classified into three subtypes: α_{1A}, α_{1B}, and α_{1D}.[7-10] These receptors are located in the smooth muscle cell membrane of the peripheral blood vessels, as well as in various nonvascular smooth muscle and non-muscular tissues.[8-12] The alpha-adrenergic blocking agents lower blood pressure by acting peripherally to dilate the blood vessels. They also cause rapid relaxation of smooth muscle in the bladder neck, prostate capsule and prostatic urethra.[11,13]

The alpha-adrenergic blocking agents 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 September 2008.

Table 1. Alpha-Adrenergic Blocking Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Doxazosin	extended-release tablet, tablet	Cardura®*, Cardura XL®	doxazosin
Prazosin	capsule	Minipress®*	prazosin
Terazosin	capsule	N/A	terazosin

*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 alpha-adrenergic blocking agents are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Alpha-Adrenergic Blocking Agents

Clinical Guideline	Recommendation(s)
European Association of Urology (EAU): **Guidelines on Benign Prostatic Hyperplasia[78] (2004)**	• Men with mild to moderate LUTS with low levels of bother are suitable for watchful waiting. • It has been shown that 5-alpha reductase inhibitors reduce prostate volume and improve symptom scores and flow rates. Maximum benefits are seen after 6 months. • Men with small prostates (<40 ml) are less likely to benefit from

Clinical Guideline	Recommendation(s)
	finasteride. • The 5-alpha reductase inhibitors can alter the natural history of symptomatic BPH by influencing prostatectomy and acute urinary retention rates. • The long-term (up to 10 years) effects of 5-alpha reductase inhibitors are substantial. • The combination of a 5-alpha reductase inhibitor with an alpha-blocker seems beneficial according to the data currently available. • Treatment with 5-alpha reductase inhibitors does not mask the detection of prostate carcinoma. • Alpha-blocker therapy can result in a rapid improvement in symptoms by a factor of 20-50% and an improvement in the flow rate of 20-30%. • Long-term data are limited but suggest that the benefits of treatment are sustained. If a patient does not experience an improvement in symptoms after an 8-week trial, treatment should be discontinued. • Patients should be informed about the side-effects of alpha-blocker therapy and the need for long-term use. • There is no difference in efficacy between different alpha-blockers.
American Urological Association (AUA): **Guideline on Management of Benign Prostatic Hyperplasia (BPH)[25] (2003)**	Mild Symptoms of BPH • A period of physician monitoring and no active intervention ("watchful watching") is recommended for patients with mild symptoms of BPH (AUA symptom score ≤7) and patients with moderate or severe symptoms (AUA symptom score ≥8) who are not bothered by their symptoms or who have not yet developed complications of BPH (e.g., renal insufficiency, urinary retention, or recurrent infection). Moderate-to-Severe Symptoms of BPH • The guidelines consider the four long-acting α_1-blockers, alfuzosin, doxazosin, tamsulosin, and terazosin, to have equal clinical effectiveness. • The α-reductase inhibitors are considered for patients with bothersome symptoms and demonstrable prostatic enlargement. • α-reductase inhibitors may also be considered for patients with symptomatic prostatic enlargement without bothersome symptoms to prevent progression of the disease. • Combination therapy with an alpha-adrenergic blocking agent plus an α-reductase inhibitor may also be considered for patients with bothersome symptoms and demonstrable prostatic enlargement.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management[21] (2009)**	• The use of the alpha-adrenergic blocking agents was not addressed in this guideline.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[19] (2007)**	• The use of the alpha-adrenergic blocking agents was not addressed in this guideline.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in**	• If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-adrenergic blocking agent (β-blocker) or a selective alpha-adrenergic blocking agent.

Clinical Guideline	Recommendation(s)
Primary Care: Pharmacological Update[20] (2006)	
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[14] (2004)**	• The alpha-adrenergic blocking agents may be useful in patients with prostatism.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[24] (2004)**	• The use of the alpha-adrenergic blocking agents was not addressed in this guideline.
World Health Organization (WHO)/International Society of Hypertension (ISH): **WHO/ISH Statement on Management of Hypertension[18] (2003)**	• The alpha-adrenergic blocking agents may be useful in patients with prostatism.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans[23] (2003)**	• The use of the alpha-adrenergic blocking agents was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[22] (2010)**	• During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they can cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the alpha-adrenergic blocking 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 Alpha-Adrenergic Blocking Agents[1-6]

Indication	Doxazosin	Prazosin	Terazosin
Benign Prostatic Hyperplasia			
Treatment of signs and symptoms of benign prostatic hyperplasia	✔		✔
Hypertension			
Treatment of hypertension	✔ *†	✔ *	✔ *

*Alone or in combination with other antihypertensive agents.
†Immediate-release formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the alpha-adrenergic blocking agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Alpha-Adrenergic Blocking Agents[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Doxazosin	IR: 65 SR: 54-59	98	Liver, extensive	Renal (9) Feces (63)	15-22
Prazosin	Well absorbed	92-97	Liver (30)	Renal (3-4) Feces	2-4
Terazosin	90	90-94	Liver, extensive	Renal (10) Feces (55-60)	9-12

IR=immediate-release, SR=sustained-release

V. Drug Interactions

Significant drug interactions with the alpha-adrenergic blocking agents are listed in Table 5.

Table 5. Significant Drug Interactions with the Alpha-Adrenergic Blocking Agents[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Alpha-adrenergic blocking agents (doxazosin, prazosin, terazosin	2	Phosphodiesterase type 5 Inhibitors	Hypotension may occur when alpha blockers and phosphodiesterase type 5 inhibitors are co-administered. Alpha blockers and phosphodiesterase type 5 inhibitors may exert additive pharmacologic activity.
Prazosin	2	β-blockers	Unknown mechanism. Postural hypotension may be increased with concurrent therapy.
Prazosin	2	Verapamil	Unknown mechanism. Verapamil may increase serum prazosin concentration and increase sensitivity to prazosin-induced postural hypotension.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the alpha-adrenergic blocking agents are listed in Table 6. These agents can cause marked hypotension and syncope with sudden loss of consciousness with the first few doses. This “first-dose” effect can be minimized by administration of the first dose at bedtime. Hypotension and syncope can also occur with dose increases, addition of other antihypertensives, and therapy interruptions. The elderly are more at risk for this adverse reaction.

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

Adverse Events	Doxazosin	Prazosin	Terazosin
Cardiovascular			
Angina	<1	<1	-
Arrhythmia	1	-	<1

Adverse Events	Doxazosin	Prazosin	Terazosin
Atrial fibrillation	-	-	<1
Bradycardia	<1	-	-
Chest pain	1-2	-	<1
Edema	3-4	1	-
Flushing	1	-	-
Hypotension	1-2	-	-
Myocardial infarction	<1	<1	-
Orthostatic hypotension	<2	1	1-4
Palpitations	1-2	5	≤4
Peripheral edema	-	-	1-6
Peripheral ischemia	<1	-	-
Syncope	1-2	1	≤1
Tachycardia	<1	-	≤2
Vasodilation	-	-	<1
Central Nervous System			
Abnormal thinking	<1	-	-
Agitation	<1	-	-
Amnesia	<1	-	-
Anxiety	1	-	<1
Ataxia	1	-	-
Cerebrovascular accident	<1	-	-
Confusion	<1	-	-
Decreased energy	-	7	-
Depersonalization	<1	-	-
Depression	1	1-10	-
Dizziness	5-19	10	9-19
Drowsiness	-	8	-
Emotional lability	<1	-	-
Fatigue	8-12	-	-
Fever	<1	-	<1
Hallucinations	-	<1	-
Headache	5-14	8	-
Hypertonia	1	-	-
Insomnia	1	-	<1
Kinetic disorders	1	-	-
Migraine	<1	-	-
Narcolepsy (worsened)	-	<1	-
Nervousness	2	1-10	-
Paranoia	<1	-	-
Paresis	<1	-	-
Paresthesia	≤1	<1	≤3
Somnolence	1-5	-	4-5
Stroke	<1	-	-
Vertigo	2-4	1-10	1
Dermatological			
Alopecia	-	<1	-
Lichen planus	-	<1	-
Pallor	<1	-	-
Rash	1	1-4	<1
Pruritus	1	<1	<1
Urticaria	<1	<1	-
Endocrine and Metabolic			
Breast pain	<1	-	-
Gout	<1	-	<1

Adverse Events	Doxazosin	Prazosin	Terazosin
Gynecomastia	<1	-	-
Pancreatitis	-	<1	-
Gastrointestinal			
Abdominal pain	2	-	<1
Anorexia	<1	-	-
Appetite decreased	<1	-	-
Cholestasis	<1	-	-
Constipation	1	1-10	<1
Diarrhea	2	1-10	<1
Dyspepsia	1-2	-	<1
Fecal incontinence	<1	-	-
Flatulence	1	-	<1
Gastroenteritis	<1	-	-
Nausea	1-3	5	2-4
Vomiting	<1	1-10	<1
Xerostomia	2	1-10	<1
Genitourinary			
Hematuria	<1	-	-
Impotence	1	<1	≤2
Libido decreased	-	-	<1
Micturition abnormality	<1	-	-
Nocturia	<1	-	-
Polyuria	2	-	<1
Priapism	<1	<1	<1
Renal calculus	<1	-	-
Sexual dysfunction	2	-	-
Urinary frequency	-	1-5	-
Urinary incontinence	1	-	<1
Urinary tract infection	1	-	<1
Hematologic			
Leukopenia	<1	<1	-
Neutropenia	<1	-	-
Purpura	<1	-	-
Thrombocytopenia	<1	-	<1
Hepatic			
Jaundice	<1	-	-
Liver function tests increased	<1	-	-
Laboratory Test Abnormalities			
Hypokalemia	<1	-	-
Musculoskeletal			
Arthralgia	1	-	<1
Arthritis	1	-	<1
Back pain	2-3	-	≤2
Cataplexy	-	<1	-
Extremity pain	-	-	<1
Joint disorder	-	-	<1
Muscle cramps	1	-	-
Muscle weakness	1	-	7-11
Myalgia	1	-	<1
Neck pain	-	-	<1
Pain	2	-	-
Shoulder pain	-	-	<1
Weakness	<1	7	-
Respiratory			

Adverse Events	Doxazosin	Prazosin	Terazosin
Bronchitis	-	-	<1
Bronchospasm	<1	-	-
Cough	-	-	<1
Dyspnea	1-3	1-10	2-3
Epistaxis	1	1-10	<1
Hepatitis	<1	-	-
Nasal congestion	-	1-10	2-6
Pharyngitis	-	-	<1
Respiratory disorder	1	-	-
Respiratory tract infection	5	-	-
Rhinitis	3	-	<1
Sinusitis	-	-	≤3
Special Senses			
Abnormal vision	1-2	-	<1
Blurred vision	-	1-10	≤2
Cataracts	-	<1	-
Conjunctivitis	1	-	<1
Hypoesthesia	<1	-	-
Intraoperative floppy iris syndrome	<1	<1	<1
Pigmentary mottling and serous retinopathy	-	<1	-
Sclera reddened	-	1-10	-
Tinnitus	1	<1	<1
Parosmia	<1	-	-
Other			
Allergic reaction	<1	<1	<1
Anaphylaxis	-	-	<1
Diaphoresis	1	-	<1
Facial edema	1	-	<1
Infection	<1	-	-
Influenza-like symptoms	1	-	≤2
Lymphadenopathy	<1	-	-
Rigors	<1	-	-
Systemic lupus erythematosus	-	<1	-
Vasculitis	-	<1	-

✓ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the alpha-adrenergic blocking agents are listed in Table 7. Treatment should be initiated at bedtime and at the lowest dose to minimize the likelihood of the "first-dose" effect. Dosages should be titrated up slowly to achieve the desired response. If therapy is interrupted for more than a few days, the initial dosing regimen and titration schedule should be reinstituted. Other antihypertensive agents should be added cautiously to reduce the risk of developing significant hypotension.

Table 7. Usual Dosing Regimens for the Alpha-Adrenergic Blocking Agents[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Doxazosin	Benign Prostatic Hyperplasia: IR initial: 1 mg once daily; maintenance: 1 to 8 mg once daily; maximum: 8 mg/day SR initial: 4 mg once daily; maintenance: 4 to 8 mg daily;	Safety and efficacy in children have not been established.	Tablet (IR): 1 mg 2 mg 4 mg 8 mg Tablet (SR):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum: 8 mg/day Hypertension: IR initial: 1 mg once daily; maintenance: 1 to 16 mg once daily; maximum: 16 mg/day		4 mg 8 mg
Prazosin	Hypertension: Initial: 1 mg 2 to 3 times a day; maintenance: 6 to 15 mg/day in 2 to 4 divided doses; maximum: 40 mg/day	Safety and efficacy in children have not been established.	Capsule: 1 mg 2 mg 5 mg
Terazosin	Benign Prostatic Hyperplasia: Initial: 1 mg at bedtime; maintenance: 1 to 10 mg/day; maximum: 20 mg/day Hypertension: Initial : 1 mg at bedtime; maintenance: 1 to 20 mg once daily; maximum: 20 mg/day	Safety and efficacy in children have not been established.	Capsule: 1 mg 2 mg 5 mg 10 mg

IR=immediate-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the alpha-adrenergic blocking agents are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Alpha-Adrenergic Blocking Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Benign Prostatic Hyperplasia				
Samli et al.[62] (2004) Doxazosin 8 mg QD vs terazosin 10 mg QD	RA, XO Men with LUTS associated with BPH	N=50 3 months	Primary: IPSS, maximum urinary flow rate	Primary: A total of 44% of the subjects in the doxazosin arm and 40% in the terazosin arm showed improvement in both IPSS and maximum urinary flow rate. After 3 months of treatment, both treatment groups resulted in an increased maximum urinary flow rate (P<0.001) and a decreased IPSS (P<0.01). A total of 19 subjects did not show improvement and switched to the other treatment drug. Of these subjects, 2/19 showed improvement in both IPSS and maximum urinary flow rate, 2/19 showed improvement in IPSS only but not in maximum urinary flow rate, 15/19 did not show any improvement.
Kaplan et al.[63] (1997) Doxazosin 4 to 8 mg QD vs terazosin 5 to 10 mg QD	OL, PRO Men with BPH and >80 years of age	N=36 6 months	Primary: Peak urinary flow rate, AUA SS	Primary: There was significant improvement in maximum urinary flow rate (P<0.008) and AUA SS (P<0.01) in both treatment groups. There were small, non-significant decreases in blood pressure.
Kaplan et al.[64] (1995) Doxazosin 4 mg QAM (DOX-AM) vs doxazosin 4 mg	PI, RA Normotensive men with symptomatic prostatism	N=43 4 to 17 months	Primary: Boyarsky symptom score, peak urinary flow rate, blood pressure, and occurrence of adverse events	Primary: There were significant improvements from baseline in Boyarsky symptom score and maximum urinary flow rate in all four treatment groups (P<0.05). There was no significant difference in Boyarsky symptom score and maximum urinary flow rate improvement between the four groups. Adverse events were significantly decreased in groups with evening

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QPM (DOX-PM) vs terazosin 5 mg QAM (TER-AM) vs terazosin 5 mg QPM (TER-PM)				administration dosing schedule (P<0.05).
Bozlu et al.[65] (2004) Doxazosin 4 mg QD vs terazosin 5 mg QD vs alfuzosin 2.5 mg TID vs tamsulosin 0.4 mg QD	RETRO Patients with LUTS suggestive of BPH with and without diabetes	N=281 6 months	Primary: Symptoms and bother score according to the Turkish validation of the IPSS, maximum flow rate, post-void residual urine volume	Primary: α1-blockers significantly improved the IPSS, bother score, maximum urinary flow rate, and post-void residual urine volume compared with baseline (P<0.001). IPSS and bother score were significantly improved more in the diabetic patients compared with the nondiabetic patients (P<0.01). There was no significant difference among the groups in the improvement rates of any of the parameters (P>0.05).
Xue et al.[66] (2007) Doxazosin 4 mg QD (controlled-release formulation)	RCT Chinese men with confirmed BPH	N=117 8 weeks	Primary: Efficacy, safety	Primary: Both drugs significantly improved the IPSS (total, irritative subscore, and obstructive subscore. P=0.001 for all) and maximum urinary flow rate (P=0.001). Other differences between groups were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tamsulosin 0.2 mg QD				
Rahardjo et al.[67] (2006) Doxazosin 2 mg QD vs tamsulosin 0.2 mg QD	MC, OL, RA Patients with LUTS due to BPH	N=101 6 weeks	Primary: IPSS, maximal urinary flow rate, average urinary flow rate and residual urine; safety	Primary: The total IPSS decreased significantly in both the tamsulosin and doxazosin groups compared to baseline (P<0.001). There was a significant difference in the decrease in total IPSS between two groups (P=0.036). Maximal urinary flow rate, average urinary flow rate and residual urine significantly improved only in the tamsulosin group (P<0.001, P<0.001, and P<0.05, respectively). There were no significant differences in SBP, DBP or heart rate profile in the tamsulosin group; however, doxazosin resulted in a significant difference from baseline in SBP (P<0.01) but not in DBP (P=NS) at the end of the study. Tamsulosin was well tolerated; only three patients (6%) in the tamsulosin group reported an adverse event (dizziness) while 11 patients (22%) in the doxazosin group reported an adverse event (dizziness), one of whom withdrew from the study.
Pompeo et al.[68] (2006) Doxazosin GITS 4 mg QD vs tamsulosin 0.4 mg QID	DB, DD, RA Brazilian patients with BPH	N=165 12 week	Primary: Absolute and percentage change from baseline in symptoms measured by IPSS Secondary: QOL question from the IPSS, questions 6 and 7 of the SFAQ	Primary: Doxazosin GITS and tamsulosin improved IPSS with no significant differences between groups at week 12. During weeks 4 to 8, tamsulosin-treated patients demonstrated a slower improvement (P<0.001) in IPSS than doxazosin GITS-treated patients. Secondary: The proportion of satisfied patients did not change over the course of the study with doxazosin GITS, while it did change significantly between weeks 4 and 8 with tamsulosin (P=0.006); this suggests that a change for the better was observed earlier with doxazosin. At week 12, the proportion of patients with little or no difficulty at ejaculation (question 6 of SFAQ) was higher in the doxazosin GITS group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.019). Both treatments were well tolerated.
Johnson et al.[69] (2007) Doxazosin (2, 4, 8 mg) QD vs finasteride 5 mg QD vs doxazosin (2, 4, 8 mg) QD and finasteride 5 mg QD vs placebo	PC, RA Men with LUTS suggestive of BPH	N=3,047 4 years	Primary: Efficacy (mean reduction in self-reported nightly nocturia at 1 and 4 years)	Primary: The number of men reporting 1 or more episodes of nocturia who finished 12 or more months of the trial came to a total of 2,583. Mean nocturia was similar in all groups at baseline. Mean nocturia was reduced at 1 year by 0.35, 0.40, 0.54 and 0.58 in the placebo, finasteride, doxazosin and combination groups, respectively. Reductions with doxazosin and combination therapy were statistically greater than with placebo (P<0.05). At 4 years, nocturia was also significantly reduced in patients treated with doxazosin and combination therapy (P<0.05 vs placebo). In men older than 70 years (n=495) all drugs significantly reduced nocturia at 1 year (finasteride 0.29, doxazosin 0.46 and combination 0.42) compared to placebo (0.11; P<0.05).
Crawford et al.[70] (2006) Doxazosin 4 to 8 mg QD vs finasteride 5 mg QD vs doxazosin 4 to 8 mg QD and	PC, RA Men with LUTS suggestive of BPH	N=737 4 years	Primary: Time to overall clinical progression of BPH, defined as either a confirmed 4-point or greater increase in AUA SS, acute urinary retention, incontinence, renal insufficiency, or recurrent urinary tract infection	Primary: The rate of overall clinical progression of BPH events in the placebo group was 4.5 per 100 person-years, for a cumulative incidence (among men who had at least 4 years of followup data) of 17%. The risk of BPH progression was significantly greater in patients on placebo with a baseline TPV of ≥31 mL vs those with a baseline TPV <31 mL (P<0.0001). The risk of BPH progression was significantly greater in patients on placebo with a baseline PSA of ≥1.6 ng/dL vs those with a baseline PSA <1.6 ng/dL (P=0.0009). The risk of BPH progression was significantly greater in patients on placebo with, a baseline maximal urinary flow rate of less than 10.6 mL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
finasteride 5 mg QD vs placebo				per second vs those with a baseline maximal urinary flow rate ≥10.6 mL per second (P=0.011) The risk of BPH progression was significantly greater in patients on placebo with a baseline PVR of ≥39 mL vs those with a baseline PVR less than 39 mL (P=0.0008). The risk of BPH progression was significantly greater in patients on placebo with baseline age ≥62 years or older vs those aged <62 years (P=0.0002).
Kaplan et al.[71] (2006) Doxazosin 4 to 8 mg QD vs finasteride 5 mg QD vs doxazosin 4 to 8 mg QD and finasteride 5 mg QD vs placebo	RCT, DB, PC Men with LUTS suggestive of BPH	N=3,047 4 years	Primary: Overall clinical progression of BPH (defined as a confirmed 4 point or greater increase in AUA SS, acute urinary retention, incontinence, renal insufficiency or recurrent urinary tract infection) Secondary: Need for invasive therapy for BPH, AUA SS, maximum urinary flow rate with time	Primary: In patients with a small prostate (baseline TPV >25 mL) combination therapy was no better than doxazosin alone for decreasing the risk of clinical progression of BPH and need for invasive therapy as well as improving AUA SS and the maximum urinary flow rate. However, in patients with moderate size (25 to >40 mL) or enlarged (≥40 mL) glands, combination therapy led to a clinical benefit in these outcomes that was superior to that of doxazosin or finasteride (P<0.05). Secondary: In men with baseline TPV <25 mL, there was no significant difference in the risk of invasive therapy for combination therapy relative to doxazosin or finasteride alone. However, in the baseline TPV subgroups of 25 to <40 mL and ≥40 mL there was a significant and marked percent risk decrease in invasive therapy, of around 60% to 80% for combination therapy vs doxazosin alone (P<0.05). In men with baseline TPV <25 mL the improvement at year 4 in AUA SS for combination therapy relative to doxazosin alone was not significantly different, whereas the improvement for combination therapy vs finasteride alone was significantly different in favor of combination therapy (P<0.05). In the baseline TPV subgroups of 25 to <40 mL and ≥40 mL, the improvement in AUA SS with combination therapy was significantly better than that for doxazosin alone and finasteride alone (P<0.05).
Kaplan et al.[76] (2008)	RCT, DB, PC	N=3,047	Primary: Total prostate	Primary: Long-term treatment with finasteride alone or in combination with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin 4 to 8 mg daily vs finasteride 5 mg daily vs doxazosin 4 to 8 mg daily and finasteride 5 mg daily vs placebo	Men ≥50 years of age with an AUA SS of 8 to 30 and a Q_{max} of 4 to 15 ml/second with a voided volume of at least 125 ml	Mean 4.5 years	volume (TPV)	doxazosin led to a consistent reduction in TPV of approximately 25% compared to placebo in men with a relatively small prostate (baseline TPV less than 25 ml and 25 to 30 ml) as well as those with a moderate size (greater than 30 to less than 40 ml) or enlarged prostate (40 ml or greater).
Djavan et al.[61] (1999) Doxazosin vs terazosin vs alfuzosin vs tamsulosin	MA Men with LUTS suggestive of benign prostatic obstruction	N=6,333 (placebo-controlled trials) N=507 (comparative trials)	Primary: Total symptom score and maximum urinary flow rate, tolerability	Primary: There was no difference in efficacy among the four drugs. Alfuzosin immediate release 2.5 mg three times daily, alfuzosin sustained-release 5 mg twice daily, terazosin 5 to 10 mg daily, doxazosin 4 to 8 mg daily, and tamsulosin 0.4 mg daily all produced comparable improvements in LUTS and maximum urinary flow rate. The total symptom score improved by 30% to 40% and the maximum urinary flow rate (Q_{max}) by 16% to 25%. Alfuzosin and tamsulosin were better tolerated than terazosin and doxazosin. Alfuzosin and tamsulosin had similar study withdrawal rates as placebo. With terazosin and doxazosin, an additional 4% to 10% of patients withdrew from the study due to intolerability. Tamsulosin had less effect on blood pressure than alfuzosin. Tamsulosin also caused less symptomatic orthostatic hypotension than terazosin.
Nickel et al.[74] (2008)	MA	26 trials	Primary: Vascular-related	Primary: Treatment with A1Bs was associated with a significant increase in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin 4 to 8 mg daily vs terazosin 1 to 10 mg daily vs alfuzosin 10 mg daily vs tamsulosin 0.4 mg daily vs placebo	Men with benign prostatic hyperplasia	4 weeks to 4.5 years	adverse events with alpha1-adrenergic blockers (A1Bs) including dizziness, hypotension, or syncope Secondary: Efficacy based on change from baseline of maximum urinary flow rate (Qmax) and change from baseline of AUA-SI or IPSS	development of a vascular-related adverse event compared to placebo (OR 2.54; 95% CI, 2.00–3.23; P<0.0001). There was a higher risk of developing the primary composite end-point compared to placebo for alfuzosin (P=0.005), terazosin (P<0.0001), doxazosin (P<0.0001) and doxazosin GITS (P<0.0001). Secondary: A1Bs improved Q_{max} by 1.32 ml/min compared to placebo (95% CI, 1.07 to 1.57; P<0.0001). The WMD in AUASI/IPSS for all A1Bs was -1.92 points compared to placebo (95% CI, -2.71 to -1.14); P<0.0001).
Tsujii et al.[72] (2000) Prazosin 0.5 to 1 mg BID vs terazosin 0.5 to 1 mg BID vs tamsulosin 0.1 to 0.2 QD	R, XO Patients with symptomatic BPH	N=121 4 weeks	Primary: Symptom score, changes in maximum and average urinary flow rate, postvoid residual urine volume, and blood pressure	Primary: The terazosin-treated group showed significant improvement in 4 out of 9 symptoms compared with tamsulosin (P<0.05). There were significant increases in maximum urinary flow rate with the prazosin group, and in average urinary flow rate with the tamsulosin groups (P<0.05). There were no significant changes in residual urine volume with any of the treatment groups. Significant blood pressure reductions were observed in the hypertensive subjects in the prazosin, terazosin, and tamsulosin groups (P<0.05 for all). In the normotensive subjects, no significant changes in blood pressure were observed with any of the drugs.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tsai et al.[73] (2007) Group A: Terazosin (generic) 1 - 4 mg QD during period 1 and terazosin (brand ®) 1 - 4 mg QD in period 2 (6 weeks) vs Group B: Terazosin (brand) 1 - 4 mg QD during period 1 and terazosin (generic) 1 - 4 mg QD in period 2 (6 weeks)	CO, OL, RA Adult men in Taiwan newly diagnosed with symptomatic BPH who had not previously received treatment for BPH	N=53 13 weeks	Primary: IPSS, tolerability (using physical examination, including vital signs; laboratory analysis; and spontaneous reporting)	Primary: At 2 and 6 weeks, no significant between-product differences were found in mean (SD) decreases from baseline in IPSS total score (generic, 2.46 [0.84] and 2.46 [1.00], respectively; branded, 1.56 [0.60] and 2.87 [0.71]) (P=0.29). At week 6, the between-product difference in mean (SD) increase from baseline in maximal uroflow rate was non-significant (generic, 2.36 [0.90] mL/s; branded, 2.03 [0.62] mL/s) (P=0.72). A total of 86 treatment-emergent adverse events were reported (45 with the generic drug; 41 with the branded drug), all of which were considered by the investigator as non-serious except for 1 case of acute epididymitis, which occurred with the generic drug. The most common adverse events reported with the generic and branded formulations were dizziness (7/48 [14.6%] and 10/50 [20.0%], respectively) and peripheral edema (1/48 [2.1%] and 3/50 [6.0%]). No significant differences in the prevalence of adverse events were found between the 2 treatments.
Yang et al.[15] (2007) Terazosin 2 mg QD for 1 week Those patients with continued LUTS after the initial treatment were allocated randomly into two groups: terazosin 2 mg QD	COMBO Patients diagnosed with LUTS due to BPH	N=69 7 weeks	Primary: IPSS	Primary: The IPSS were significantly improved in both groups after treatment, and the reduction of IPSS in the combination group was significantly greater than that in the terazosin group (P<0.01). A decrease in urgency, frequency and nocturia were the main contributory factors causing the reduction of IPSS in the combination group. The differences about the peak urinary flow rate and the residual urine from the baseline values were noted in both groups after treatment, but were not significant between the two groups. The incidence of adverse effects in the combination group was higher than that in the terazosin group. As expected, the most common adverse effect was mouth dryness, which is associated with anticholinergic drugs such as tolterodine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for six weeks vs terazosin 2 mg QD and tolterodine 2 mg BID for six weeks				
Dong et al.[77] (2009) Terazosin vs tamsulosin	MA Patients with benign prostatic hyperplasia (BPH)	N=2,816 (12 trials) 4 weeks	Primary: International prostate symptom score (IPSS), quality of life (QOL), maximum urinary flow rate (Q_{max}), average urinary flow rate (Q_{ave}), residual volume, prostate volume, and adverse effects	Primary: After 4 weeks of treatment, tamsulosin demonstrated a significant improvement in IPSS compared to terazosin (WMD -1.24; 95% CI, -1.98 to -0.51; P=0.0009). There was no significant difference in QOL between the treatment groups (WMD -0.04; 95% CI, -0.16 to 0.24), Q_{max} (WMD -0.38; 95% CI, -1.18 to 0.41), Q_{ave} (WMD -0.39; 95% CI, -0.84 to 0.06), residual volume (WMD -4.32; 95% CI, -10.96 to 2.33), or prostate volume (WMD -0.28; 95% CI, -3.37 to 2.81). Fewer patients experienced dizziness (RR=0.38; 95% CI, 0.30 to 0.48), severe hypotension (RR=0.16; 95% CI, 0.04 to 0.68), and dry mouth (RR=0.14; 95% CI, 0.03 to 0.77) with tamsulosin compared to patients receiving terazosin.
Liu et al.[75] (2009) Terazosin 2 mg daily vs amlodipine 5 mg daily vs terazosin 2 mg and	RCT, DB, PG Men ≥50 years of age with Stage 1 or 2 essential hypertension (systolic blood pressure 140 to 180 mm Hg and/or diastolic blood pressure 90 to 110 mm Hg) and with LUTS (International	N=360 28 days	Primary: Reduction in the total and sub-scores of the International Prostate Symptom Score and blood pressure	Primary: Treatment with terazosin and amlodipine monotherapy led to a similar reduction in the total IPSS (6.7 vs 6.9). There were no significant difference in the reduction in the bladder outlet obstruction (BOO) sub-score (4.0 vs 4.1), OAB sub-score (2.9 vs 2.6), or QOL score (1.1 vs 1.2) with amlodipine compared to terazosin. Treatment with terazosin + amlodipine led to a greater reduction in the QOL score (1.4 vs 1.1, P<0.05) compared to amlodipine monotherapy. There was no significant difference in the reduction in the total IPSS (7.8), BOO sub-score (4.8), or OAB sub-score (3.2) with terazosin + amlodipine compared with to amlodipine alone or terazosin alone. The rate of the responders (defined as patients with a reduction of 40% or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5 mg daily	Prostate Symptom Score [IPSS] ≥10)			more in the total IPSS, BOO sub-score, OAB sub-score, or QOL score or total IPSS of <8) were similar between the amlodipine group (36.1%, 41.2%, 46.2%, and 33.6%, respectively) and terazosin group (39.3%, 46.2%, 39.3%, and 41.0%, respectively). The rate of responders in the OAB sub-score was significantly greater in the terazosin + amlodipine group than in the terazosin group (53.8% vs 39.3%, P<0.05). The rate of responders in the QOL score was significantly greater in the terazosin + amlodipine group than in the amlodipine group (47.1% vs 33.6%, P<0.05). The mean reduction in SBP and DBP was greater with amlodipine than terazosin (21.8/10.0 vs 11.9/6.5 mm Hg, P<0.01). The greatest reduction in SBP and DBP (25.2/12.6 mm Hg) occurred in the terazosin + amlodipine group (P<0.01 vs terazosin and P<0.05 vs amlodipine). The rates of blood pressure control were greater in the amlodipine group (63.9%) and the terazosin + amlodipine group (73.1%) than in the terazosin group (36.8%, both P<0.001).
Hypertension				
Hayduk et al.[27] (1987) Doxazosin 1 to 16 mg QD vs terazosin 1 to 20 mg QD	DB, MC, RA Patients with high blood pressure	N=55 14 weeks	Primary: Blood pressure (success defined as decrease in standing DBP to <90 mm Hg and by 5 mm Hg or at least a 10 mm Hg reduction in standing DBP; normalized blood pressure defined by DBP ≤90 mm Hg)	Primary: Therapeutic success was higher in the doxazosin treated group compared with the terazosin treated group (73% vs 64%). At endpoint, there were more subjects with normalized blood pressure in the doxazosin group compared with the terazosin group (65% vs 57%). The incidence of treatment-related side effects was higher in terazosin group compared with the doxazosin group (39% vs 30%).
Torvik et al.[28] (1986) Doxazosin 1 to 16 mg QD	DB Patients with essential hypertension	N=172 12 weeks	Primary: Blood pressure, heart rate, plasma lipid profiles	Primary: Doxazosin and prazosin both produced significant reductions in blood pressures compared with placebo (P<0.05 to P<0.005). There was no significant difference between the three groups in plasma lipid profiles or heart rate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs prazosin 0.5 to 10 mg BID vs placebo				There was a significant decrease in triglycerides from baseline in the doxazosin treated group only (P<0.05).
Fukiyama et al.[29] (1991) Doxazosin vs prazosin	DB, MC, RA Patients with essential hypertension	N=126 12 weeks	Primary: Blood pressure, heart rate	Primary: There was no significant difference between the groups in blood pressure reduction (P=0.7826). Both drugs produced significant decreases in blood pressure from baseline (P<0.001). No significant changes in heart rate were observed.
DePlanque et al.[30] (1991) Doxazosin QD vs prazosin BID	DB, DD, PG Patients with mild or moderate essential hypertension not adequately controlled by diuretics and β-blockers	N=43 14 weeks	Primary: Blood, heart rate, serum lipid levels, calculated coronary heart disease risk using the Framingham equation	Primary: There was no statistically significant difference between the groups in SBP (P=NS), heart rate (P=NS), or serum lipid levels. Doxazosin showed a significantly greater reduction in standing (P=0.01) and supine (P=0.04) DBP compared with prazosin. 84.2% of the doxazosin treated group and 56.5% of the prazosin treated group achieved therapeutic success. Doxazosin (P=0.02) showed a greater reduction from baseline in the calculated risk of coronary heart disease than prazosin (P=NS).
Deger et al.[31] (1986) Prazosin BID vs terazosin QD	DB, MC, PC Patients with mild to moderate hypertension	N=174 14 weeks	Primary: Blood pressure, heart rate	Primary: Terazosin produced significant reduction in supine and standing DBP when compared to placebo (P≤0.05). Prazosin did not produce a significant reduction in supine DBP, but did produce a significant reduction in mean standing DBP when compared to placebo. There was no significant difference in heart rate changes between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				treatment groups.
Ruoff et al.[32] (1986) <u>Study 1:</u> Prazosin vs terazosin vs placebo <u>Study 2:</u> Terazosin vs HCTZ <u>Study 3:</u> Terazosin and HCTZ vs prazosin and HCTZ	DB, PG, RA Patients with mild to moderate hypertension	Study 1 N=54 Study 2 N=37 Study 3 N=28	Primary: Blood pressure, pulse rate, body weight, laboratory tests, physical examinations, electrocardiograms	Primary: Study 1- There was no significant difference in blood pressure changes between the terazosin and prazosin treatment groups. Study 2- HCTZ produced a significantly greater reduction in supine DBP compared with terazosin. There were no significant differences in standing blood pressure between the HCTZ and terazosin treatment groups. Study 3- There were no significant differences in blood pressure between the treatment groups. The drug treatments did not produce significant changes in pulse rates, body weights, laboratory test results, physical examinations, or electrocardiograms.
Neaton et al.[35] (1993) TOMHS	DB, MC, PC, RA Patients with mild hypertension (DBP <100 mm Hg)	N=902 4.4 years	Primary: Blood pressure, quality of life, side effects, blood lipid levels and analysis	Primary: There was a significant reduction in blood pressure in all the active treatment groups compared with placebo (–15.9 vs –9.1 mm Hg for SBP and –12.3 vs –8.6 mm Hg for DBP; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin 2 to 4 mg QD vs chlorthalidone 15 to 30 mg QD vs acebutolol 400 mg QD vs amlodipine 5 mg QD vs enalapril 5 to 10 mg QD vs placebo			of other serum components, echocardiographic changes, and incidence of cardiovascular events	There were no major differences in blood pressure lowering between the 5 active treatment groups (P=0.10). Total cholesterol was significantly reduced more in the doxazosin group than in the amlodipine, chlorthalidone, and placebo groups (P<0.01). The reduction in LDL-C was significantly more in doxazosin group than in the amlodipine, chlorthalidone, and placebo groups. Reduction in triglycerides was significantly larger with the doxazosin, enalapril, and amlodipine groups than acebutolol group (P<0.01). The lowest level of fasting insulin was observed with doxazosin; fasting insulin was lower than placebo in all drug groups.
Liebson et al.[36] (1995) TOMHS Doxazosin vs chlorthalidone	DB, PC, RA Patients with mild hypertension	N=844 4 years	Primary: Changes in blood pressure and pulse, changes in left ventricular mass from baseline to end of study period as assessed by echocardiograms	Primary: All drug treatment groups showed significantly greater reduction of blood pressure compared with placebo (mean decrease of 16/12 vs 9/9 mm Hg; P<0.001). Pulse rate decreased by 10 bpm for the acebutolol group compared with 1 to 3 bpm for the other treatment groups. All drug treatment groups and the placebo group showed significant decreases (10% to 15%) in left ventricular mass. The chlorthalidone group showed the largest decrease in left ventricular mass at 34 g compared to 24

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs acebutolol vs amlodipine vs enalapril vs placebo				to 27 g for the other treatment groups.
Brown et al.[38] (1995) <u>Study A:</u> Doxazosin, followed by amlodipine, followed by doxazosin and amlodipine vs <u>Study B:</u> Enalapril, followed by amlodipine, followed by enalapril and amlodipine	DB, RA, TW, XO Patients with moderate or severe hypertension	N=24 18 weeks	Primary: Blood pressure and heart rate, foot volume as measure of edema, plasma noradrenaline concentration	Primary: <u>Study A:</u> The decrease in blood pressure was significantly greater than the sum of the blood pressure falls at the end of the single drug treatment periods. The reduction in blood pressure was greater with amlodipine than doxazosin (P<0.01). The reduction in blood pressure was greater with combination than amlodipine (P<0.001). No significant changes in heart rate were observed. One subject developed ankle edema. The plasma noradrenaline concentration did not change significantly during the single drug treatment periods, but doubled at the end of the combination treatment period (P<0.05). <u>Study B:</u> The reduction in blood pressure was significantly greater with amlodipine than enalapril (P<0.05). The reduction in blood pressure was significantly greater with combination than amlodipine (P<0.05) with the exception of erect blood pressure. No significant changes in heart rate were noted. No significant difference in foot volume was observed between treatments. The plasma noradrenaline was significantly higher than at baseline (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Deary et al.[39] (2002) Doxazosin 1 to 4 mg vs amlodipine 5 mg vs lisinopril 2.5 to 10 mg vs bisoprolol 5 mg vs bendro-flumethiazide 2.5 mg vs placebo	DB, LSR, XO Hypertensive patients, aged 18 to 55 years old	N=34 42 weeks (6 week treatment of each drug or placebo, then the 7th week was a repeat of each patient's most effective, tolerated drug)	Primary: Blood pressure and heart rate	Primary: All drug treatments caused significant decreases in blood pressure. Bendroflumethiazide performed significantly worse (P=0.0016) and bisoprolol performed significantly better (P=0.004) than amlodipine. When the most effective drugs for each patient were tabulated, all drugs included in the study except for bendroflumethiazide, were represented.
Hayduk et al.[40] (1987) Study 1: Doxazosin 1 to 16 mg QD vs	DB, MC Patients with hypertension	Study 1: N=903 10 to 24 week trial; therapy continued for up to 62 weeks Study 2:	Primary: Blood pressure, heart rate	Primary: Blood pressure lowering effect of doxazosin was similar to that of the other antihypertensive drugs. There was no significant difference in the heart rate with the doxazosin treated group. The β-blockers demonstrated clinically significant bradycardia. Both doxazosin and terazosin were equally efficacious, but doxazosin was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prazosin 1 to 20 mg BID vs HCTZ 25 to 100 mg QD vs nadolol 40 to 160 mg QD vs atenolol 50 to 100 mg QD vs metoprolol 100 to 200 mg BID vs placebo <u>Study 2:</u> Doxazosin 16 mg QD vs terazosin 20 mg QD		N=52 12 weeks		effective at significantly lower doses.
Trost et al.[41] (1987)	DB, MC, PG	N=104	Primary: Blood pressure and	Primary: There was no significant difference in the supine and standing blood

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doxazosin 1 to 16 mg QD vs HCTZ 25 to 100 mg QD	Patients with hypertension	6 months	serum lipid changes	pressures between the two treatment groups. There was significantly greater reduction in total triglyceride (P=0.002) and total cholesterol concentration (P=0.006) and significantly greater increase in HDL-C:total cholesterol ratio (P=0.001) in the doxazosin arm compared with the HCTZ arm.
Grimm et al.[42] (1996) Doxazosin 2 to 16 mg vs HCTZ 25 to 50 mg	DB, PG, RA Patients with hypertension	N=107 1 year	Primary: Blood pressure, heart rate, biochemistries, lipids/lipoproteins, QOL, echocardiograms, adverse effects	Primary: There were no significant differences in blood pressure lowering, heart rate, QOL measures, or serious adverse effects between the two treatment groups. The doxazosin treated group experienced a more favorable high density lipoprotein /total cholesterol ratio (P≤0.01) compared with the hydrochlorothiazide group. Both drug treatments showed significant reduction in left ventricular mass (P<0.001) and wall thickness (P<0.05). The left ventricular systolic and diastolic internal dimensions were significantly less in the HCTZ group compared with the doxazosin group.
Ferrara et al.[43] (1993) Doxazosin 1 to 16 mg QD vs captopril 25 to 150 mg QD	MC, OL, PG Patients with hypercholesterolemia and hypertension	N=224 14 weeks	Primary: Blood pressure (normalized blood pressure defined as standing diastolic pressure ≤90 mm Hg), serum lipid levels, quality of life	Primary: Blood pressure was significantly reduced with both drugs (P<0.001). A total of 73% of the doxazosin group and 67% of the captopril group achieved normalized blood pressure. Serum total cholesterol level was significantly improved with both drugs (P<0.001). The HDL-C concentration was only significantly increased in the doxazosin group (P<0.001). The calculated 10-year risk for the development of coronary heart disease was significantly reduced with both drug treatments (P<0.001).
Derosa et al.[44] (2005) Doxazosin 4 mg	DB, PG, RA Patients with type 2 diabetes and mild	N=96 1 year	Primary: Blood pressure, glucose metabolism and	Primary: Blood pressure was significantly reduced in both treatment groups compared with baseline (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs irbesartan 300 mg QD	hypertension		lipid parameters	Irbesartan was significantly better in lowering blood pressure compared to doxazosin (P<0.05). Doxazosin significantly reduced glycosylated hemoglobin, fasting plasma glucose, fasting plasma insulin, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides (P≤0.05 for all parameters). As monotherapy, neither of the drugs achieved adequate blood pressure control.
Taylor et al.[45] (1988) Doxazosin 1 to 16 mg QD vs enalapril 10 to 40 mg QD	DB, PG Patients with mild or moderate essential hypertension	N=67 18 weeks	Primary: Blood pressure (therapeutic success defined as standing DBP ≤90 mm Hg), lipid parameters	Primary: A total of 74% of the doxazosin group achieved therapeutic success compared with 81% of the enalapril group. Blood pressures were significantly reduced in both groups. There were no significant changes in the lipid profile observed for either drug.
Wessels et al.[46] (1991) Doxazosin QD vs enalapril QD	DB, DD, PC, RA Patients with mild or moderate essential hypertension	N=54 12 weeks	Primary: Blood pressure, heart rate, serum lipid profile, calculated coronary heart disease risk	Primary: Both drugs produced significant reductions in blood pressure (P<0.05). There was no significant change in heart rate with both drugs. Doxazosin showed a significant reduction in the total serum cholesterol concentration (P<0.05). Doxazosin also showed a decrease in triglyceride level (P=NS) and an increase in HDL-C/total cholesterol ratio (P=NS). Coronary heart disease risk reduction was significant and greater in the doxazosin group compared with the enalapril group (–27.58% vs –18.49%, P<0.02).
Hjortdahl et al.[47] (1987) Doxazosin QD	DB, RA Patients with mild to moderate essential	N=115 24 weeks	Primary: Blood pressure, heart rate, lipid profile, and side effects	Primary: There was no significant difference between treatment groups for blood pressure and heart rate except HCTZ produced significantly greater supine SBP than doxazosin (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs HCTZ QD	hypertension			There were significant reductions in total cholesterol (P=0.006) and total triglycerides (P=0.018) for the doxazosin group. 11 patients of the HCTZ group had an abnormally low potassium level and 7 of the HCTZ treated group had abnormally high uric acid concentrations.
Ott et al.[48] (1987) Doxazosin 1 to 16 mg QD vs atenolol 50 to 100 mg QD	DB, MC, RA Patients with mild to moderate hypertension	N=126 20 weeks	Primary: Blood pressure, heart rate	Primary: There was no significant difference between treatment groups in blood pressure. Both drugs reduced heart rate, but atenolol produced a significantly greater decrease in heart rate than doxazosin (P<0.001).
Frick et al.[49] (1986) Doxazosin 1 to 16 mg QD vs atenolol 50 to 100 mg QD	DB, DD, MC, RA Patients with mild to moderate essential hypertension	N=152 1 year	Primary: Blood pressure, heart rate, lipid profile	Primary: At endpoint, there was greater blood pressure reduction with atenolol than doxazosin. This was statistically significant only in the supine position (P<0.05). Doxazosin reduced the heart rate slightly, while atenolol produced a marked bradycardia (P<0.0001). High density lipoprotein /total cholesterol ratio was raised in the doxazosin group and lowered in the atenolol group (P=0.001). Triglyceride levels decreased in the doxazosin group and increased in the atenolol group (–5.0% vs +42.7%; P<0.001).
Daae et al.[50] (1998) Doxazosin QD vs atenolol QD	DB, MC, PG Patients with mild to moderate hypertension	N=228 1 year followed by a 4-year open-label extension phase	Primary: Blood pressure, heart rate, lipid profile, calculated risk of developing coronary heart disease in ten years using the Framingham	Primary: Both groups showed similar decreases in blood pressure. The doxazosin-treated group had a significantly greater reduction from baseline in coronary heart disease risk than the atenolol-treated group (P<0.05). Total cholesterol significantly decreased from baseline in both treatment groups (P≤0.05), with no statistically significant difference between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			equation	groups. HDL–C (P<0.01), the HDL-C:total cholesterol ratio (P<0.01), and triglyceride levels (P<0.01) significantly improved in the doxazosin group compared with the atenolol group.
Talseth et al.[51] (1991) Doxazosin (mean dose used: 5.2 mg QD) vs atenolol (mean dose used: 66.4 mg QD)	PG, RA Patients with mild and moderate hypertension	N=164 3 years	Primary: Blood pressure, heart rate, lipids profile, calculated coronary heart disease risk using the Framingham equation	Primary: Both drugs produced similar reductions in blood pressure. Atenolol produced a significant decrease in heart rate (P<0.05), while doxazosin did not change the heart rate significantly. Doxazosin significantly reduced triglyceride levels (P<0.001), increased HDL-C levels (P<0.001), and increased the HDL-C:total cholesterol ratio (P<0.001) compared with atenolol. The calculated coronary heart disease risk was significantly increased with atenolol (P<0.05) and significantly decreased with doxazosin (P<0.05) from baseline.
Carruthers et al.[52] (1993) Doxazosin QD vs atenolol QD	COMP, RA Patients with mild to moderate systemic hypertension and normal serum lipid	N=191 24 weeks	Primary: Calculated coronary artery disease risk using the Framingham formula	Primary: Doxazosin treatment produced a significantly greater reduction in coronary heart disease risk compared with atenolol (P=0.0074). The relative risk of coronary heart disease was reduced to 0.92 in the atenolol group (P=0.144) and 0.74 in the doxazosin group (P=0.0001) from baseline.
Searle et al.[53] (1990) Doxazosin 11 mg (mean dose) QD and atenolol 100 mg QD vs placebo and	DB, MC, RA Patients with mild to moderate essential hypertension	N=87 12 weeks	Primary: Blood pressure reduction, heart rate change, change in serum lipids	Primary: Blood pressure significantly decreased in the atenolol-doxazosin–treated group compared with the atenolol-placebo–treated group (17.0/12.3 vs 6.2/6.7 mm Hg; P<0.05). The supine blood pressure was decreased by 13.2/9.8 mm Hg in the atenolol-doxazosin–treated group compared with 9.2/6.0 mm Hg in the atenolol-placebo–treated group (P=NS). Only minor, insignificant changes in serum lipids and no significant changes in heart rate were observed between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atenolol 100 mg QD				
Ohta et al.[54] (2007) Doxazosin 1 to 2 mg QD to BID added to combination of calcium-channel blockers and angiotensin II receptor blocker or angiotensin converting enzyme inhibitors	RETRO Hypertensive patients that showed poor blood pressure control	N=41 3 months (mean follow-up 170 days)	Primary: Blood pressure, blood chemistry	Primary: Blood pressure decreased from 152±14/81±12 to 135±14/70±11 mm Hg after the addition of doxazosin at a mean dose of 1.5 mg/day (P<0.001). When good SBP control was defined as <140 mm Hg, the prevalence of patients with good SBP control increased from 24% to 61% (P<0.01). Similarly, the prevalence of patients with good DBP control (<90 mm Hg) increased from 78% to 98% (P<0.01). Patients whose SBP decreased more than 10 mm Hg (n=25) showed significantly higher baseline SBP, serum total cholesterol and low-density lipoprotein cholesterol levels compared to those who showed less SBP reduction (<10 mm Hg; P<0.01). Comparable blood pressure reductions were obtained between obese patients (body mass index ≥25, change in blood pressure (Δ blood pressure) at 3 months: -15±15/-12±9 mm Hg, n=18) and nonobese patients (BMI<25, Δ blood pressure: -14±19/-7±8 mm Hg, n=23) patients.
de Alvaro et al.[55] (2006) ASOCIA Doxazosin GITS 4 to 8 mg QD (added to entry medication)	MC, PRO, NC Patients with hypertension (≥140/≥90 mm Hg) on previous antihypertensive medication that was uncontrolled	N=3,631 16 weeks	Primary: Goal blood pressure (<140/<90 mm Hg), adverse events	Primary: The proportion of patients reaching goal (<140/<90 mm Hg) after 4 weeks of add-on therapy with doxazosin GITS was 39% and increased to 61% at Week 16. SBP and DBP (mean ± SEM) decreased, respectively, from 161.6 ± 0.2 and 95.1 ± 0.1 mm Hg at baseline to 142.2 ± 0.2 and 84.1 ± 0.1 mm Hg at Week 4 (P<0.0001) and 136.8 ± 0.2 and 80.6 ± 0.2 mm Hg at Week 16 (P<0.0001). Adverse events occurred in 108 patients (3.0%), with 57 (1.6%) related to the study treatment. In 17 patients (0.5%), serious adverse events were described, but only one was related to the study drug.
Os et al.[60] (2006) Doxazosin 4 mg QD	DB, PG, RA Male or female patients aged 18 to	N=310 9 weeks	Primary: Efficacy, safety	Primary: All groups had a significant decrease in blood pressure at all study visits compared with baseline. The proportion of patients who reached goal sitting DBP (<90 mm Hg) was similar among the three treatment groups, except at Week 1, when more patients in the doxazosin GITS group had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs doxazosin 2 mg QD vs doxazosin GITS 4 mg QD	80 diagnosed with mild-to-moderate essential hypertension (sitting DBP 95 to 110 mm Hg and SBP <180 mm Hg)			obtained the goal compared with those in the doxazosin 2mg group (40.6% vs 22.3%; P=0.005). The proportion of patients who reached sitting SBP (<140 mm Hg) goal was similar among groups. Adverse event profiles among the groups were similar.
Materson et al.[57] (1994) Prazosin 4 to 20 mg QD vs HCTZ 12.5 to 50 mg QD vs atenolol 25 to 100 mg QD vs captopril 25 to 100 mg QD vs clonidine 0.2 to 0.6 mg QD vs	DB, MC, RA Men with DBP of 95 to 109 mm Hg	N=1,292 1 year	Primary: Success as defined by DBP ≤95 mm Hg at one year	Primary: Success rates were 59% for diltiazem, 51% for atenolol, 50% for clonidine, 46% for HCTZ, 42% for captopril, 42% for prazosin, and 25% for placebo (P<0.001 between diltiazem and HCTZ, atenolol and prazosin). The rates of adverse effects leading to termination of treatment were highest with prazosin at 13.8% and clonidine at 10.1%, which was significantly different from captopril at 4.8%, atenolol at 2.2%, HCTZ at 1.1%, diltiazem at 5.5%, and placebo at 6.4%. Successful blood pressure control was highest with diltiazem at 64% in African Americans, highest with captopril at 55% in younger whites, and highest with atenolol at 68% in older whites.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diltiazem SR 120 to 360 mg QD vs placebo				
Chrysant et al.[58] (1986) Terazosin vs placebo (in combination with other antihypertensive agents)	DB, MC, PC, RA, Patients with inadequate control of essential hypertension	N=138 Duration not specified	Primary: Blood pressure, physical examination, electrocardiograms	Primary: There was a significant mean reduction in supine DBP with the terazosin treated group compared with placebo (–7.3 vs -0.6 mm Hg; P<0.05). There were no significant changes between treatment groups in physical examinations or electrocardiograms.
Holtzman et al.[59] (1988) Terazosin vs placebo in combination with atenolol	DB, MC, PC Patients with hypertension	N=92 10 weeks	Primary: Blood pressure, lipids profile	Primary: There was a statistically significant reduction in supine and standing blood pressure (P<0.05), total cholesterol (P<0.05) and LDL-C plus very low density lipoprotein cholesterol levels (P<0.05) with the terazosin treated group.
Outcomes Trials				
ALLHAT[16,33-34] (2000, 2003, 2004) Doxazosin 2 to 8 mg QD vs	AC, DB, RA Subjects ≥55 years of age with hypertension and had at least one cardiac risk factor	N=24,335 3.3 years	Primary: Combined occurrence of fatal coronary heart disease or nonfatal myocardial infarction	Primary: There was no difference in risk of fatal coronary heart disease or nonfatal myocardial infarction (P=0.71) or total mortality (P=0.56) between the chlorthalidone and doxazosin treatment group. Secondary: The doxazosin group compared with the chlorthalidone group had a higher

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlorthalidone 12.5 to 25 mg QD			Secondary: All-cause mortality, stroke, combined CVD	risk of stroke (RR, 1.19; 95% CI, 1.01 to 1.40; P=0.04) and combined CVD (RR, 1.25; 95% CI, 1.17 to 1.33; P<0.001). Congestive heart failure risk was doubled in the doxazosin group compared with the chlorthalidone group (P<0.001), and the RR was 1.16 (P<0.001) for angina, 1.15 (P=0.05) for coronary revascularization, and 1.07 (P=0.50) for peripheral arterial disease. Mean SBP in the doxazosin group was about 2 to 3 mm Hg higher than in the chlorthalidone group, while the mean DBP was the same. There was a greater reduction in SBP in those treated with chlorthalidone compared with doxazosin (P<0.01 in patients with newly diagnosed with diabetes or with no glucose disorder; P=NS for patients with known diabetes). The doxazosin group compared with the chlorthalidone group had an increased heart failure risk (RR, 1.85; 95% CI, 1.56 to 2.19 in patients with known diabetes mellitus and RR, 1.63; 95% CI, 1.05 to 2.55 in the patients with newly diagnosed glucose disorder).
Wright et al.[56] (2008) ALLHAT Doxazosin vs chlorthalidone vs amlodipine vs	RA, DB Hypertensive individuals with and without MetS	N=42,418 3.2 years (median follow-up)	Primary: Fatal coronary heart disease or nonfatal myocardial infarction Secondary: Heart failure, combined CVD, stroke, end-stage renal disease	Primary: No differences were noted among the four treatment groups, regardless of race or MetS status for the primary end point (fatal coronary heart disease or nonfatal myocardial infarction). Secondary: Significantly higher rates of heart failure were consistent across all treatment comparisons in those with MetS. Relative risks were 1.50 (95% CI, 1.18 to 1.90), 1.49 (1.17 to 1.90), and 1.88 (1.42 to 2.47) in African American participants and 1.25 (1.06 to 1.47), 1.20 (1.01 to 1.41), and 0.82 (1.51 to 2.19) in non–African American participants for amlodipine, lisinopril, and doxazosin comparisons with chlorthalidone, respectively. Higher rates for combined CVD were observed with lisinopril-chlorthalidone (RR, 1.24; 95% CI, 1.09 to 1.40; RR, 1.10; 95% CI, 1.02 to 1.19, respectively) and doxazosin-chlorthalidone comparisons (RR, 1.37; 95% CI, 1.19 to 1.58; RR, 1.18; 95% CI, 1.08 to 1.30, respectively) in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lisinopril				African American and non–African American participants with MetS. Higher rates of stroke were seen in African American participants only (RR, 1.37; 95% CI, 1.07 to 1.76 for the lisinopril-chlorthalidone comparison, and RR, 1.49; 95% CI, 1.09 to 2.03 for the doxazosin-chlorthalidone comparison). African American patients with MetS also had higher rates of end-stage renal disease (RR, 1.70; 95% CI, 1.13 to 2.55) with lisinopril compared with chlorthalidone.
Dahlöf et al.[37] (2005) ASCOT-BPLA Amlodipine 5 to 10 mg and if needed perindopril 4 to 8 mg or atenolol 50 to 100 mg and if needed bendro-flumethiazide 1.25 to 2.5 mg If goal blood pressure was still not achieved, doxazosin 4 to 8 mg was added to the regimen.	RCT, MC Patients with hypertension	N=19,257 5.5 years	Primary: Nonfatal myocardial infarction and fatal coronary heart disease Secondary: Nonfatal myocardial infraction, and fatal coronary heart disease, total coronary endpoint, total cardiovascular events and procedures, all-cause mortality, cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, silent myocardial infarction, unstable angina, chronic stable angina, peripheral arterial	Primary: The trial was halted early due to findings that patients on the amlodipine-perindopril regimen had fewer of the primary endpoints (P=0.1052) and lower rates of fatal and nonfatal stroke (P=0.0003), total cardiovascular events and procedures (P<0.0001), all-cause mortality (P=0.025), and incidence of developing diabetes (P<0.0001). There was a greater reduction in blood pressure by an average of 2.7/1.9 mm Hg in the amlodipine-based regimen compared with the atenolol-based regimen. There was no significant difference in the percent of patients (25%) that stopped therapy because of an adverse event between the two treatment groups. However, a significantly greater proportion of patients in the amlodipine-based regimen stopped the trial therapy early because of serious adverse events compared with the atenolol-based regimen (P<0.0001). Secondary: Patients on the amlodipine-perindopril regimen had fewer fatal and nonfatal strokes (P=0.0003), total cardiovascular events and procedures (P<0.0001), and all-cause mortality (P=0.025). Patients on the amlodipine-perindopril regimen had less chance of developing diabetes (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			disease, life-threatening arrhythmias, development of diabetes mellitus, development of renal impairment	

Drug regimen abbreviations: BID=twice daily, QAM=once in the morning, QD=once daily, QID=four times a day, QPM=once in the evening, SR=sustained-release, TID=three times a day
Study abbreviations: AC=active-controlled, CI=confidence interval, COMP=comparative, CON=controlled, DB=double-blind, DD=double-dummy, LSR= Latin-square randomization, MA= Meta-analysis, MC=multi-center, NC=non-comparative, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, PI=pilot study, PRO=prospective, RA=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SD=standard deviation, TW=three-way, XO=crossover
Miscellaneous abbreviations: AUA SS=American Urological Association symptom score, β-blockers=β-adrenergic blocking agents, BPH=Benign Prostatic Hyperplasia, bpm=beats per minute, CVD=cardiovascular disease, DBP=diastolic blood pressure, GITS=gastrointestinal therapeutic system, HCTZ=hydrochlorothiazide, HDL-C=high-density lipoprotein cholesterol, IPSS=International Prostatic Symptom Score, LDL-C =low-density lipoprotein cholesterol, LUTS=lower urinary tract symptoms, MetS=cardiometabolic syndrome, PSA=Prostate specific antigen, PVR=post-void residual urine volume, Qmax=maximum urinary flow rate, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SFAQ=Sexual Function Abbreviated Questionnaire, TPV=total prostate volume, WMD=weighted mean difference

Additional Evidence

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

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

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

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For 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 Alpha-Adrenergic Blocking Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Doxazosin	extended-release tablet, tablet	Cardura®*, Cardura XL®	$-$$$	$
Prazosin	capsule	Minipress®*	$-$$$$	$-$$
Terazosin	capsule	N/A	N/A	$

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

X. Conclusions

The alpha-adrenergic blocking agents are approved for the treatment of benign prostatic hyperplasia (BPH) and hypertension.[1-6] All of the agents are available in a generic formulation. Guidelines on the management of BPH recommend the use of an alpha-adrenergic blocking agent or a 5α-reductase inhibitor in patients with moderate-to-severe symptoms.[25,78] Alpha-blockers can quickly improve symptoms and flow rate, while the 5α-reductase inhibitors have the potential for long-term reduction in prostate volume. Available data suggests that the combination is also effective. Clinical trials have demonstrated similar efficacy among the various alpha-adrenergic blocking agents for the treatment of BPH.[25,61-65,72-73,78]

There are several national and international organizations that have published guidelines on the treatment of hypertension. Most of the guidelines do not address the use of the alpha-adrenergic blocking agents. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[14,18,20,24] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[19,21] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[19,21] All of the available guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.

Several clinical trials have shown that the alpha-adrenergic blocking agents effectively lower blood pressure when administered as monotherapy or in combination with other antihypertensive agents.[27-32,35-36,39-51,53,55,58-60,75] Comparative studies have demonstrated similar efficacy when the alpha-blockers were directly compared to each other, as well as when they were compared to ACE inhibitors, β-blockers, calcium-channel blocking agents and thiazide-type diuretics.[29-30,32,35,40-42,47-48,50-51] The ALLHAT trial evaluated the effects of doxazosin on cardiovascular morbidity and mortality.[16,33-34] Treatment with doxazosin increased the risk of stroke and cardiovascular events; however, it provided other benefits including improvements in insulin resistance and lipid parameters.

There is insufficient evidence to support that one brand alpha-adrenergic blocking agent 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 alpha-adrenergic blocking 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 alpha-adrenergic blocking 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
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Beta-Adrenergic Blocking Agents
AHFS Class 242400
November 10, 2010

I. Overview

The beta-adrenergic blocking agents (β-blockers) are approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, migraine prophylaxis, myocardial infarction and pheochromocytoma.[1-27] These agents differ with regards to their adrenergic-receptor blocking, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1-3] There are at least three distinct types of β receptors distributed throughout the body (β_1, β_2 and β_3). β_1 receptors are located predominantly in the heart and kidneys. β_2 receptors are located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle and skeletal muscle. β_3-receptors are located in fat cells. β-blockers primarily exert their effects through a blockade of β_1 and β_2 receptor subtypes. Agents that have a greater affinity for β_1 receptors are considered to be cardioselective. These agents may be safer in patients with asthma, chronic obstructive pulmonary disease and peripheral vascular disease because they produce less inhibition of β_2 receptors, which mediate vasoconstriction and bronchospasm. Cardioselectivity is dose dependent; therefore, β_2 blockade can occur at higher doses with these agents.[1] Carvedilol and labetalol also block α-adrenergic receptors, which would be expected to reduce peripheral vascular resistance to a greater extent than other β-blockers.

The β-blockers are available as single entity agents, as well as fixed-dose combination products. Each of the combination products contains a thiazide-type diuretic. The thiazide-type diuretics inhibit the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.

The beta-adrenergic blocking agents that are included in this review are listed in Table 1 and comparative information on cardioselectivity is highlighted in Table 2. This review encompasses all dosage forms and strengths. All of the agents are available in a generic formulation, with the exception of nebivolol and penbutolol. This class was last reviewed in September 2008.

Table 1. Beta-Adrenergic Blocking Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Acebutolol	capsule	Sectral®*	acebutolol
Atenolol	tablet	Tenormin®*	atenolol
Atenolol and chlorthalidone	tablet	Tenoretic®*	atenolol and chlorthalidone
Betaxolol	tablet	Kerlone®*	betaxolol
Bisoprolol	tablet	Zebeta®*	bisoprolol
Bisoprolol and hydrochlorothiazide	tablet	Ziac®*	bisoprolol and hydrochlorothiazide
Carvedilol	extended-release capsule, tablet	Coreg®*, Coreg CR®	carvedilol
Esmolol	injection^	Brevibloc®*	none
Labetalol	injection, tablet	Trandate®*	labetalol
Metoprolol	extended-release tablet, injection, tablet	Lopressor®*, Toprol-XL®*	metoprolol
Metoprolol and hydrochlorothiazide	tablet	Lopressor HCT®*	metoprolol and hydrochlorothiazide
Nadolol	tablet	Corgard®*	nadolol
Nadolol and bendroflumethiazide	tablet	Corzide®*	nadolol and bendroflumethiazide
Nebivolol	tablet	Bystolic®	none
Penbutolol	tablet	Levatol®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Pindolol	tablet	N/A	pindolol
Propranolol	extended-release capsule, injection, solution, tablet	Inderal LA®*, InnoPran XL®	propranolol
Propranolol and hydrochlorothiazide	tablet	N/A	propranolol and hydrochlorothiazide
Sotalol	injection, tablet	Betapace®*, Betapace AF®*	sotalol
Timolol	tablet	N/A	timolol

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
PDL=Preferred Drug List
N/A=Not available

Table 2. Selected Pharmacologic Properties of the Beta-Adrenergic Blocking Agents[1-27]

Generic Name(s)	Adrenergic-Receptor Blocking Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity
Acebutolol	β_1*	+†	+
Atenolol	β_1*	0	0
Betaxolol	β_1*	+	0
Bisoprolol	β_1*	0	0
Carvedilol	α_1 - β_1 - β_2	++	0
Labetalol	α_1 - β_1 - β_2	0	+
Metoprolol	β_1*	0†	0
Nadolol	β_1 - β_2	0	0
Nebivolol	β_1*	0	0
Penbutolol	β_1 - β_2	0	+
Pindolol	β_1 - β_2	+	++
Propranolol	β_1 - β_2	++	0
Sotalol	β_1 - β_2	0	0
Timolol	β_1 - β_2	0	0

0=none; +=low; ++=moderate; +++ high
*Inhibits β_2 receptors (bronchial and vascular) at higher doses.
†Detectable only at doses much greater than required for β blockade.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the beta-adrenergic blocking agents are summarized in Table 3. For a more comprehensive overview of the pharmacologic management of acute myocardial infarction, angina pectoris, heart failure and hypertension, please refer to the Appendix.

Table 3. Treatment Guidelines Using the Beta-Adrenergic Blocking Agents

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation[45] (2008)**	Prophylactic Therapies in the Acute Phase • Routine intravenous administration of a β-blocker is not indicated. An oral β-blocker should be given as soon as the patient is stable. • At discharge and in the absence of contraindications, all patients should be treated with ASA, a thienopyridine, a β-blocker and a statin. In patients with significant LV dysfunction, an ACE inhibitor (or an ARB) should be added. With the exception of the thienopyridine, these medications should be given indefinitely. Secondary Prevention • Oral β-blockers for all patients, regardless of blood pressure or LV function, unless contraindicated.
American College of Cardiology (ACC)/American Heart	Initial and Hospital Management • Oxygen, morphine, nitroglycerin (NTG), angiotensin-converting

Clinical Guideline	Recommendation(s)
Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI)**[43] **(2007)**	enzyme inhibitors (ACE inhibitors), β-blockers, and aspirin may be used in patients presenting with a myocardial infarction (MI). Patients should be considered for reperfusion therapy. • Patients that did not receive β-blockers within 24 hours of ST-Elevation Myocardial Infarction (STEMI) should be started on these agents unless contraindicated. • Patients with early contraindications to β-blockers within 24 hours of STEMI should be reevaluated for candidacy for β-blocker therapy as secondary therapy. • All patients should continue receiving β-blockers unless contraindicated. Secondary Prevention • For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with β-blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or LV dysfunction with or without HF symptoms, unless contraindicated.
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction**[44] **(2007)**	Secondary Prevention • All patients who have had an acute MI should be offered treatment with a combination of the following drugs: ACE inhibitor, aspirin, β - blocker, and statin. • After an acute MI, all patients without left ventricular systolic dysfunction or with left ventricular systolic dysfunction should be offered treatment with a β-blocker. • β-blockers should be continued indefinitely after an acute MI. • After a proven MI in the past, asymptomatic patients with preserved left ventricular function should not routinely be offered a β-blocker unless they are at risk for further cardiovascular events or other compelling indications exist.
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**[46] **(2007)**	• Patients with hypertension and established coronary artery disease should be treated with blood pressure medication(s) as tolerated, including ACE inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 mm Hg or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • β-blocker therapy is recommended indefinitely in all patients who have had an MI, ACS, or left ventricular dysfunction with or without heart failure symptoms unless contraindicated.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris**[48] **(2006)**	Therapy to Improve Prognosis • β-blockers are recommended as first-line therapy in patients with angina in the absence of contraindications. Symptomatic Treatment and Treatment of Ischemia • β-blockers should be titrated to full dose. Considerations should be given for 24-hour prophylaxis against ischemia. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB. Treatment of Syndrome X • Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination.
American College of Physicians (ACP): **Primary Care**	Symptomatic Patients • The following agents are recommended to prevent MI or death and to

Clinical Guideline	Recommendation(s)
Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease[50] (2004)	reduce symptoms: aspirin (clopidogrel may be used in patients intolerant to aspirin), β-blockers, statins, and ACE inhibitors. • The following agents are recommended to reduce symptoms only: NTG (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful. Asymptomatic Patients With Evidence Suggesting CAD on Previous Testing • The following agents should be used to prevent MI and death: aspirin (in patients with a previous MI), β-blockers (in patients with a previous MI), statins (in patients with type 2 diabetes or documented CAD), and an ACE inhibitor (in patients with documented CAD and diabetes, systolic dysfunction, or both).
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[47] (2007)**	Early Hospital Care • Oral β-blocker therapy should be initiated within the first 24 hours for patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk for cardiogenic shock, or 4) other relative contraindications to beta blockade. • It is reasonable to administer intravenous β-blockers at the time of presentation for hypertension to patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk for cardiogenic shock, or 4) other relative contraindications to beta blockade. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge • β-blockers are recommended in all patients unless otherwise contraindicated. Treatment should be initiated acutely or within a few days of the event and continued indefinitely. In patients with moderate-to-severe left ventricular failure, β-blockers should be titrated gradually. • It is reasonable to prescribe β-blockers to low-risk patients (i.e., normal LV function, revascularized, no high-risk features) recovering from UA/NSTEMI in the absence of absolute contraindications. • For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with chronic kidney disease or diabetes), it is useful to add blood pressure medication(s) as tolerated, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazide diuretics as needed to achieve target blood pressure. Cardiovascular "Syndrome X" • Nitrates, β-blockers, and calcium-channel blockers (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)[49] (2007)**	Acute Treatment • β-blockers are recommended in most patients (in the absence of contraindications), especially in patients with hypertension or tachycardia. Long-term Management • β-blockers should be initiated in all patients with left ventricular dysfunction.
American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC): **Guidelines for Management of Patients with Atrial**	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.

Clinical Guideline	Recommendation(s)
Fibrillation[63] (2006)	• 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. <u>Pharmacological Rate Control During Atrial Fibrillation</u> • 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. • 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. • When the ventricular rate cannot be adequately controlled both at rest 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. • 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>Cardioversion of Atrial Fibrillation</u> • Digoxin and sotalol may be harmful when used for pharmacological cardioversion of atrial fibrillation and are not recommended. • 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. <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

Clinical Guideline	Recommendation(s)
	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. • 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> • Prophylactic administration of sotalol may be considered for patients at risk of developing atrial fibrillation following cardiac surgery. • 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**[140] **(2006)**	• 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. • 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 fibrillation. • 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.

Clinical Guideline	Recommendation(s)
	• 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. • 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. • Patients receiving β-blocker therapy prior to cardiothoracic surgery should continue their therapy unless indicated otherwise.
American College of Chest Physicians (ACCP): **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery**[141] **(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. • 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.
American Academy of Family Physicians (AAFP)/American College of Physicians (ACP): **Management of Newly Detected Atrial Fibrillation**[142] **(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. • 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. • 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 Society of Cardiology (ESC): **Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death**[64] **(2006)**	<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. • 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

Clinical Guideline	Recommendation(s)
	amiodarone, may be used in patients with ICDs who have recurrent VT/ventricular fibrillation (VF) with frequent appropriate ICD firing. Ventricular Arrhythmia and Sudden Cardiac Death Related to Specific Pathology • 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. 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 • 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, 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: 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 • Drug therapy with β-blockers and/or calcium-channel blockers can be useful in patients with structurally normal hearts with symptomatic

Clinical Guideline	Recommendation(s)
	VT arising from the right ventricle. Ventricular Arrhythmias and Sudden Cardiac Death Related to Specific Populations • 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.
American College of Cardiology (ACC)/European Society of Cardiology (ESC): **Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy[67] (2003)**	• β-blockers are a preferred drug treatment strategy for symptomatic patients with outflow gradients present only with exertion. • Propranolol was the first agent used in the treatment of hypertrophic cardiomyopathy (HCM); more recently, extended release propranolol and other agents including atenolol, metoprolol, and nadolol are used. • There is no standardized consensus on the selection of medications for particular patients. The medication chosen for treatment is based largely on the preferences of individual practitioners, investigators, and centers. • For the initial medical treatment of exertional dyspnea, verapamil or a β-blocker may be used. Verapamil may be instituted in those who have failed β-blocker therapy or who have asthma. • Currently, there is no data demonstrating that using verapamil and a β-blocker concurrently offers any benefits compared to monotherapy with either agent. • Due to the potential for disopyramide to increase ventricular rate during AF, it is recommended to concurrently administer a low dose β-blocker to obtain a normal resting heart rate. • In patients with end-stage HCM, there is a lack of evidence demonstrating that β-blocker prevents or convey a benefit to congestive heart failure and ventricular systolic dysfunction, ultimately, these patients may become transplant candidates. • The use of β-blockers, verapamil or disopyramide for prophylaxis of symptoms in asymptomatic patients is still questionable. • β-blockers or verapamil may be used to slow AV nodal conduction during the programming of a pacemaker. • There is a lack of data demonstrating the efficacy of β-blockers, verapamil and type IA antiarrhythmics for prophylaxis of sudden cardiac death (SCD) in asymptomatic HCM patients; an ICD is more effective at preventing SCD. • Management of sinus rhythm in patients with HCM is strongly recommended and β-blockers, verapamil and digoxin have proven to be effective in controlling heart rate in chronic AF.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline[52] (2010)**	Patients With Risk Factors for Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure • β-blockers are recommended in patients who have had an MI to reduce mortality, recurrent MI, and prevent heart failure. Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction • β-blocker therapy should be considered in asymptomatic patients with reduced LVEF. Patients With Left Ventricular Systolic Dysfunction • β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with an LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40% post-MI and non post-MI. • β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status

Clinical Guideline	Recommendation(s)
	and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients. • β-blocker therapy is recommended in the majority of patients with heart failure and reduced LVEF, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. β-blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if β-blockers are initiated in patients with marked bradycardia or marked hypotension. β-blockers are not recommended in patients with asthma with active bronchospasm. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • β-blockers are recommended in patients with heart failure and preserved LVEF who have also had an MI, hypertension, or atrial fibrillation requiring ventricular rate control. Patients With Heart Failure and Coronary Artery Disease • β-blockers are recommended in patients with reduced LVEF or post-MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) in stable hospitalized post-MI patients with LVEF or heart failure. Patients With Heart Failure and Hypertension • The addition of a β-blocker is recommended even if blood pressure is controlled. Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended. Managing Heart Failure in Special Populations • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure and LVEF. • ACE inhibitor and β-blocker therapy are recommended in all women with symptomatic or asymptomatic heart failure and LV systolic dysfunction. ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with symptomatic or asymptomatic heart failure and LV systolic dysfunction. ARBs are recommended as substitute therapy for heart failure in African Americans intolerant of ACE inhibitors.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**[51] **(2009)**	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors, and β-blockers have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed Heart Failure Symptoms (Stage B)

Clinical Guideline	Recommendation(s)
	• β-blockers and ACE inhibitors should be used in all patients with a recent or past history of MI regardless of ejection fraction or presence of heart failure. • β-blockers and ACE inhibitors should be used in patients who have reduced left ventricular ejection fraction and do not have a history of MI or heart failure. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • β-blockers (using 1 of the 3 proven to reduce mortality; i.e., bisoprolol, carvedilol, or extended-release metoprolol) are recommended in all stable patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-blockers, ARBs, ACE inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms. Hospitalized Patients • Oral therapies known to improve outcomes (ACE inhibitors, angiotensin receptor blockers, β-blockers) should be continued during hospitalization. If not currently treated with these therapies, initiation is recommended prior to hospital discharge. • Initiation of β-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators and inotropic agents. Patients with Concomitant Disorders • Nitrates and β-blockers are recommended in patients with heart failure and angina.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[53] **(2008)**	Pharmacologic Therapy of Chronic Heart Failure • β-blockers are recommended for patients with LVEF ≤40% and mild to severe symptoms of heart failure (NYHA class II-IV). Patients with asymptomatic LV systolic dysfunction after MI also have an indication for a β-blocker. Patients should also be receiving ACE inhibitor and/or ARB therapy (and aldosterone antagonist, if indicated). • β-blockers should usually be initiated in stable patients and only with caution in recently decompensated patients (and only initiated in hospital in these patients). Arrhythmias in Chronic Heart Failure • A β-blocker or digoxin is recommended to control the heart rate at rest in patients with heart failure and LV dysfunction. • A combination of digoxin and a β-blocker may be considered to control the heart rate at rest and during exercise. Comorbidities and Special Populations • Agents with documented effects on morbidity and mortality such as ACE inhibitors, β-blockers, and ARBs are recommended in patients with co-existing pulmonary disease. The majority of patients with heart failure and COPD can safely tolerate β-blocker therapy. A history of asthma should be considered a contraindication to the use of any β-blocker.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management**[57] **(2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to

Clinical Guideline	Recommendation(s)
	protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • Despite trial evidence of outcome reduction, the β-blocker/diuretic combination favors the development of diabetes and should be avoided, unless required for other reasons, in predisposed patients. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[56] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, non dihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications,

Clinical Guideline	Recommendation(s)
	the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[58] (2006)**	• β-blockers are generally not preferred for initial therapy for hypertension, though they may be used in younger patients in the case of ACE inhibitor and ARB intolerance, in women of childbearing age, and in patients with an increased sympathetic drive. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes). • Patients who are well-controlled on a β-blocker do not need to be switched from the β-blocker to an alternative agent. • If a β-blocker is to be discontinued, the dose should be gradually decreased. β-blockers should not be discontinued in patients who have a compelling indication for β-blockade, including those with angina and those who have had an MI. • Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[54] (2004)**	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • In patients with ACS (MI or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. Other medications may be used as needed for blood pressure control. • For patients with post-MI, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are

Clinical Guideline	Recommendation(s)
	beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2-4 times higher in African American patients. • Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators. • β-blockers are useful in the treatment and/or prophylaxis of atrial arrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, and perioperative hypertension. • β-blockers should be used cautiously or avoided in patients with asthma, reactive airways disease, or second or third degree heart block. • Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • Thiazide diuretics are useful in slowing demineralization in osteoporosis.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[62] (2004)**	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.

Clinical Guideline	Recommendation(s)
	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension**[55] **(2003)**	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors). • A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[61] **(2003)**	• ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic. • All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[60] **(2010)**	• During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they can cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin.
European Federation of Neurological Societies (EFNS): **Guideline on the Drug Treatment of Migraine - Revised Report of an EFNS Task Force**[143] **(2009)**	• Prophylactic drugs for the treatment of migraine with good efficacy and tolerability and evidence of efficacy are β-blockers, calcium-channel blockers, antiepileptic drugs, NSAIDs, antidepressants, and miscellaneous drugs. • The use of all these drugs is based on empirical data rather than on proven pathophysiological concepts. • There is no commonly accepted indication for starting a prophylactic treatment. Prophylactic drug treatment of migraine should be

Clinical Guideline	Recommendation(s)
	considered and discussed with the patient when 1) the quality of life, business duties, or school attendance are severely impaired; 2) frequency of attacks per month is two or higher; 3) migraine attacks do not respond to acute drug treatment; or 4) frequent, very long, or uncomfortable auras occur. • The recommended drugs of first choice are β-blockers (metoprolol or propranolol), calcium-channel blockers (flunarizine), and antiepileptic drugs (valproic acid or topiramate). • Drugs of second choice include amitriptyline, venlafaxine, naproxen, and bisoprolol. • Drugs of third choice include acetylsalicylic acid, gabapentin, magnesium, riboflavin, coenzyme Q10, candesartan, lisinopril, and methylsergide. • β-blockers are clearly effective in migraine prophylaxis and very well studied. The best evidence has been obtained for metoprolol and propranolol. Bisoprolol, timolol and atenolol might be effective, but evidence is less convincing compared with propranolol and metoprolol. • The calcium-channel blocker, flunarizine, has been shown to be effective in migraine prophylaxis in several studies. • Valproic acid and topiramate are two antiepileptic drugs with evidence of efficacy in more than one placebo-controlled trial. The efficacy rates are comparable to those of metoprolol, propranolol, and flunarizine. Topiramate is also efficacious in the prophylaxis of chronic migraine and may have some effect in migraine with medication overuse.
American Academy of Family Physicians (AAFP)/American College of Physicians-American Society of Internal Medicine (ACP-ASIM): **Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headache[66] (2002)**	• Use nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy and migraine-specific agents (i.e., oral naratriptan or rizatriptan, SC or oral sumatriptan, and oral zolmitriptan) in patients who have failed NSAID therapy. • Preventative medications should be considered in patients who have two or more attacks per month that produce disability lasting 3 or more days per month; contraindication to, or failure of, acute treatments; use of abortive medication more than twice per week; have uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction. • Recommended first-line agents for the prevention of migraine headache are propranolol, timolol, amitriptyline, divalproex sodium, and sodium valproate.
US Headache Consortium: **Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine[144] (2000)**	General Considerations • Initiate therapy with the lowest effective dose. Begin with a low dose of the chosen pharmacological agent and increase the dose slowly until clinical benefits are achieved in the absence of adverse events or until limited by adverse events. • Give each treatment an adequate trial. A clinical benefit may take as long as two to three months to manifest itself. • Use of a long-acting formulation may improve compliance. • Some conditions are more common in persons with migraine. Take into account the presence of coexisting diseases. These include stroke, myocardial infarction, Raynaud's phenomenon, epilepsy, affective disorders, and anxiety disorders. • Once the coexisting condition has been identified, select a pharmacological agent that will treat both disorders. • Establish that the coexisting condition is not a contraindication for the selected migraine therapies.

Clinical Guideline	Recommendation(s)
	• Establish that the treatments being used for coexisting conditions do not exacerbate migraine. • Beware of interactions between pharmacological agents used for migraine and those used for other conditions. <u>β-blockers</u> • Evidence shows that propranolol is effective for the prevention of migraine. Direct comparisons demonstrated few significant differences in efficacy between propranolol and amitriptyline, naproxen sodium, mefenamic acid, divalproex sodium, and methysergide. One trial comparing propranolol and amitriptyline suggested that propranolol is more efficacious in patients with migraine alone; amitriptyline was more effective for patients with mixed migraine and tension-type headache. • Results comparing metoprolol with placebo reported mixed results. Direct comparisons of metoprolol with propranolol suggest that metoprolol is efficacious for the prevention of migraine. • Timolol, atenolol and nadolol are also likely to be beneficial based on comparisons with placebo or with propranolol. • β-blockers with intrinsic sympathomimetic activity (acebutolol and pindolol) appear to be ineffective for the prevention of migraine. • A few trials used long-acting or extended-release preparations of propranolol or metoprolol, but evidence was insufficient to determine whether these preparations were more efficacious and/or better tolerated than regular formulations of these agents.
National Cancer Institute (NCI): **Pheochromocytoma Treatment, Physician Data Query (PDQ)[65] (2008)**	• Initial treatment of pheochromocytoma following diagnosis focuses on blocking of alpha-adrenergic activity with the administration of phenoxybenzamine or an α_1-adrenergic receptor antagonist, such as prazosin. • Once alpha blockade is established, β-blockers may be used to control symptoms manifestations caused by pheochromocytoma, such as hypertension and tachyarrhythmias. • If the pheochromocytoma tumor cannot be removed, a combination of α-blockers and β-blockers may be used long-term to control symptoms.
American Academy of Neurology (AAN): **Practice Parameter: Therapies for essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology[68] (2005)**	• Propranolol and primidone are agents that are most commonly used to treat essential tremor (ET). • It is recommended that propranolol, propranolol LA, or primidone be offered to patients who want treatment for limb tremor in ET, depending on concurrent medical conditions and potential side effects. • It is recommended that either primidone or propranolol be used as initial therapy to treat limb tremor in ET. • It is recommended that atenolol and sotalol be considered for treatment of limb tremor associated with ET, and propranolol may be considered as a treatment option for head tremor in patients with ET. • Nadolol may be considered a treatment option for limb tremor associated with ET. • Pindolol is not recommended for treatment of limb tremor in ET. • Due to the lack of evidence, a recommendation regarding the use of metoprolol in the treatment of limb tremor in ET cannot be provided. • The combination of primidone and propranolol may be used to treat limb tremor when the use of a single agent does not adequately decrease tremor. • The dosages of propranolol and primidone may need to be increased after 12 months of therapy when treating limb tremor in ET.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the beta-adrenergic blocking agents are noted in Tables 4 – 5. 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 Beta-Adrenergic Blocking Agents (Drugs A – M)[4-27]

Indication	Acebutolol	Atenolol	Atenolol/ Chlorthalidone	Betaxolol	Bisoprolol	Bisoprolol/ HCTZ	Carvedilol	Labetalol	Metoprolol	Metoprolol/ HCTZ
Angina Pectoris										
Long-term management of angina pectoris		✔							✔ †§	
Arrhythmias										
Management of ventricular premature beats	✔									
Heart Failure										
Treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and to reduce the risk of hospitalization^							✔		✔ §	
Hypertension										
Treatment of hypertension	✔ *	✔ *	✔ ‡	✔ *	✔ *	✔	✔ *	✔ *	✔ *†§	✔ ‡
Myocardial Infarction										
Management of hemodynamically stable patients with acute myocardial infarction to reduce cardiovascular mortality		✔							✔ †	
Reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of <40%							✔			

HCTZ=hydrochlorothiazide
*Alone or in combination with other antihypertensive agents.
‡This fixed dose combination drug is not indicated for initial therapy of hypertension.
†Immediate-release formulation.
§Extended-release formulation.
^Usually in addition to diuretics, ACE inhibitors, and digitalis.

Table 5. FDA-Approved Indications for the Beta-Adrenergic Blocking Agents (Drugs N – T)[4-27]

Indication	Nadolol	Nadolol/ Bendro-flumethiazide	Nebivolol	Penbutolol	Pindolol	Propranolol	Propranolol/ HCTZ	Sotalol	Timolol
Angina Pectoris									
Long-term management of angina pectoris	✔								
Decrease angina frequency and increase exercise tolerance in patients with angina pectoris						✔ †§			
Arrhythmias									
Maintenance of normal sinus rhythm in patients with atrial fibrillation/flutter who are currently in sinus rhythm								✔ §§	
To control ventricular rate in patients with atrial fibrillation and a rapid ventricular response						✔ †			
Treatment of ventricular arrhythmias that are considered life-threatening								✔ **	
Hypertension									
Treatment of hypertension	✔ *	✔ ‡	✔ *	✔ *	✔ *	✔ *	✔ ‡		✔ *
Myocardial Infarction									
Reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable						✔ †			
Reduce cardiovascular mortality and risk of reinfarction in patients who have survived the acute phase of myocardial infarction and are clinically stable									✔
Miscellaneous									
Management of familial or hereditary essential tremor						✔ †			
To improve NYHA functional class in symptomatic patients with hypertrophic subaortic stenosis						✔ †§			
Prophylaxis of migraine headache						✔ †§			✔
Adjunct to alpha-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine-secreting tumors						✔ †			

HCTZ=hydrochlorothiazide
*Alone or in combination with other antihypertensive agents.
‡This fixed dose combination drug is not indicated for initial therapy of hypertension.
†Immediate-release formulation.
§Extended-release formulation (excludes InnoPran XL®).
**Betapace®
§§Betapace AF®

IV. Pharmacokinetics

The pharmacokinetic parameters of the beta-adrenergic blocking agents are listed in Table 6. The lipophilic properties vary among the agents. The higher the lipid solubility, the higher the potential to cross the blood brain barrier and increase the risk of central nervous system adverse events, including dizziness and drowsiness.[1-2]

Table 6. Pharmacokinetic Parameters of the Beta-Adrenergic Blocking Agents[4-27]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)	Lipid Solubility
Acebutolol	40	26	Liver	Renal (30-40) Bile (3-8) Feces (56)	3-4	Low
Atenolol	50	16	N/A	Renal (40-50) Feces (50)	6-7	Low
Atenolol and chlorthalidone	A: 50 C: 65	A: 16 C: 75	A: N/A C: Liver	A: Renal (40-50) Feces (50) C: Renal (60)	A: 6-7 C: 40-60	A: Low
Betaxolol	84-93	50	Liver, extensive	Renal (>80)	14-22	Low
Bisoprolol	80	30	Liver (50)	Renal (50) Feces (<2)	9-12	Low
Bisoprolol and hydrochlorothiazide	B: 80 H: 50-75	B: 30 H: 40-68	B: Liver (50)	B: Renal (50) Feces (<2) H: Renal (>95)	B: 9-12 H: 6-15	B: Low
Carvedilol	21-35	98	Liver, extensive	Renal (16) Feces (60)	6-10	Moderate
Labetalol	25	50	Liver, extensive	Renal (55-60) Feces (50)	5-8	Moderate
Metoprolol	50-77	12	Liver, extensive	Renal (95)	3-7	Moderate
Metoprolol and hydrochlorothiazide	Not reported	M: 12 H: 68	M: Liver, extensive	M: Renal (95) H: Renal (72-97)	M: 3-7 H: 10-17	M: Moderate
Nadolol	20-40	28-30	None	Renal (25) Feces (77)	20-24	Low
Nadolol and bendroflumethiazide	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Nebivolol	12-96	98	Liver, extensive	Renal (<1) Feces (13-44)	12-19	High
Penbutolol	100	80-98	Liver, extensive	Renal (90)	17-26	High
Pindolol	87-90	40-60	Liver (60-65)	Renal (35-40) Feces (6-9)	3-4	Moderate
Propranolol	30-70	93	Liver (50-70)	Renal (<1)	3-4	High
Propranolol and hydrochlorothiazide	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Sotalol	60-100	0	Liver, minor	Renal (66-75)	7-18	Low
Timolol	61	<10	Liver (80)	Renal (20)	2-4	Low-Moderate

A=atenolol, B=bisoprolol, C=chlorthalidone, H=hydrochlorothiazide, M=metoprolol, N/A=not available

V. Drug Interactions

Significant drug interactions with the beta-adrenergic blocking agents (β-blockers) are listed in Table 7.

Table 7. Significant Drug Interactions with the Beta-Adrenergic Blocking Agents[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	1	Epinephrine	Nonselective β blockade allows α -receptor effects of epinephrine to predominate. Increasing vascular resistance leads to a rise in blood pressure and reflex bradycardia.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	1	Sympathomimetics	Nonselective β-blockers may block the action of beta-agonists, potentially resulting in severe bronchospasm in asthmatics.
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	1	Verapamil	May be synergistic or additive effects. Verapamil may inhibit oxidative metabolism of certain β-blockers. Additive QT interval prolongation is possible with sotalol.
Sotalol	1	Bepridil	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
Sotalol	1	Chloroquine	Prolonged QT interval and cardiac arrhythmias are a potential when sotalol and chloroquine are coadministered.
Sotalol	1	Class IA or IC Antiarrhythmic Agents	Class IA and IC antiarrhythmics and sotalol may cause additive pharmacologic and adverse cardiovascular effects when co-administered.
Sotalol	1	Dofetilide	The risk of cardiovascular toxicity, including torsades de pointes, may be increased by co-administration of dofetilide and sotalol. Pharmacologic effects of dofetilide and sotalol on electrical conduction of the heart may be additive.
Sotalol	1	Dronedarone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
Sotalol	1	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
Sotalol	1	Fluconazole	Coadministration of fluconazole and sotalol may increase the risk of potentially fatal cardiac arrhythmias (torsades de

Generic Name(s)	Significance Level	Interaction	Mechanism
			pointes), especially in seriously ill patients and/or patients receiving high dose fluconazole.
Sotalol	1	Haloperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
Sotalol	1	Maprotiline	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
Sotalol	1	Methadone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when sotalol is co-administered with methadone.
Sotalol	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and sotalol.
Sotalol	1	Pentamidine	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when sotalol is co-administered with pentamidine.
Sotalol	1	Perflutren	Additive QT interval prolongation may occur during coadministration of perflutren and sotalol.
Sotalol	1	Phenothiazines	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and phenothiazines are co-administered.
Sotalol	1	Phosphodiesterase type 5 Inhibitors	Phosphodiesterase type 5 inhibitors and sotalol may cause additive adverse effects when co-administered. Prolonged QT interval with the potential for cardiac arrhythmias may occur.
Sotalol	1	Pimozide	Sotalol and pimozide may cause additive adverse effects when co-administered. Cardiovascular toxicity, including torsades de pointes, may occur due to additive QT-interval prolongation.
Sotalol	1	Quinolones	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
Sotalol	1	Serotonin Receptor Antagonists	The risk of QT-interval prolongation and cardiac

Generic Name(s)	Significance Level	Interaction	Mechanism
		Antiemetics	arrhythmias caused by serotonin receptor antagonist antiemetics may be increased by co-administration of sotalol.
Sotalol	1	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and sotalol.
Sotalol	1	Tyrosine Kinase Receptor Inhibitor	Additive QT interval prolongation is a possibility when tyrosine kinase receptor inhibitors are coadministered with sotalol.
Sotalol	1	Ziprasidone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and ziprasidone are co-administered.
Thiazides (hydrochlorothiazide, bendroflumethazide)	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Thiazides (hydrochlorothiazide, chlorthalidone, bendroflumethazide)	1	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Atenolol	2	Ampicillin	The bioavailability of atenolol may be decreased by impaired GI absorption induced by ampicillin.
β-blockers (metoprolol, propranolol, sotalol)	2	Amiodarone	Additive pharmacologic effects of both drugs may result in severe bradycardia, hypotension, or cardiac arrest. Possible additive QT interval prolongation with sotalol and amiodarone.
β-blockers (bisoprolol, carvedilol, metoprolol, pindolol, propranolol, timolol)	2	Cimetidine	Cimetidine may reduce hepatic first-pass extraction, decrease liver blood flow, and inhibit hepatic metabolism of β-blockers.
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	2	Clonidine	B-blocker inhibition of β_2 receptor mediated vasodilation leaves peripheral α_2-receptor mediated vasoconstriction unopposed to clonidine stimulation.
β-blockers	2	Diltiazem	Additive AV nodal blockade

Generic Name(s)	Significance Level	Interaction	Mechanism
(acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)			may lead to synergistic bradycardia
β-blockers (carvedilol, metoprolol, propranolol, timolol)	2	Diphenhydramine	Inhibition of CYP2D6-mediated β-blocker metabolism may decrease the metabolism of certain β-blockers resulting in excessive cardiovascular effects.
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, timolol)	2	Flecainide	Unknown mechanism. Combination may result in additive bradycardia and cardiac arrest
β-blockers (metoprolol, propranolol)	2	Hydralazine	Hydralazine increases systemic availability of some β-blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism.
β-blockers (bisoprolol, carvedilol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	2	Insulin	β-Blockers blunt sympathetic mediated responses to hypoglycemia.
β-blockers (atenolol, carvedilol, metoprolol, nadolol, pindolol, propranolol, sotalol)	2	Lidocaine	Reduced hepatic lidocaine metabolism and possibly a minor component of diminished hepatic blood flow.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	2	Meglitinides	Unknown mechanism. Possible increase in hypoglycemic activity of meglitinides.
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	2	Nonsteroidal Anti-inflammatory Drugs	NSAIDs may inhibit renal prostaglandin synthesis, allowing unopposed pressor systems to produce hypertension.
β-blockers (pindolol, propranolol, sotalol)	2	Phenothiazines	Chlorpromazine may inhibit the first-pass hepatic metabolism of propranolol and increase its pharmacologic effects. Certain β-blockers may inhibit the metabolism of phenothiazines increasing the risk for cardiac side effects, including torsades de pointes.
β-blockers (metoprolol, propranolol)	2	Propafenone	Propafenone increases plasma β-blocker level by decreasing first-

Generic Name(s)	Significance Level	Interaction	Mechanism
			pass metabolism and reducing systemic clearance. Both drugs are oxidized by the hepatic cytochrome P450 system, and propafenone appears to inhibit the metabolism of the β-blocker.
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	2	Quinazolines	Unknown mechanism. Additive vasodilation may increase risk of hypotension, specifically orthostatic hypotension. Generally occurs with the addition of prazosin to chronic β-blocker therapy, not β-blocker added to chronic prazosin therapy
β-blockers (atenolol, carvedilol, metoprolol, propranolol, timolol)	2	Quinidine	Oxidative metabolism of certain β-blockers may be inhibited by quinidine.
β-blockers (carvedilol, metoprolol, propranolol)	2	Rifamycins (rifabutin, rifampin, rifapentine)	Possible decrease in oral bioavailability of carvedilol resulting in first-pass metabolism.
β-blockers (metoprolol, nebivolol, propranolol, timolol)	2	Serotonin Reuptake Inhibitors	Inhibition of P-450 2D6 enzyme may decrease the metabolism of metoprolol resulting in excessive pharmacologic activity.
β-blockers (carvedilol, metoprolol, nebivolol, propranolol, timolol)	2	Terbinafine	Terbinafine inhibits P-450 2D6 and may result in increased plasma concentrations of certain β-blockers.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	2	Theophyllines	Pharmacologic antagonism. B-blockers may reduce the n-demethylation of theophylline.
β-blockers (carvedilol, metoprolol, propranolol)	2	Thioamines	Hyperthyroidism appears to cause increased clearance of β-blockers with a high extraction ration. This may be the result of increased liver blood flow, first-pass metabolism and volume of distribution.
Carvedilol	2	Cyclosporine	Unknown mechanism. Carvedilol may increase plasma concentrations of cyclosporine and dose reduction may be required.
Carvedilol	2	Digoxin	Carvedilol may increase digoxin bioavailability. Possible additive depression of myocardial conduction and decreased renal tubular digoxin secretion.
Labetalol	2	Inhalation anesthetics	Additive myocardial depressant effects possibly resulting in excessive hypotension.

Generic Name(s)	Significance Level	Interaction	Mechanism
Propranolol	2	Mefloquine	Additive slowing of cardiac conduction possibly resulting in lengthening of the QT interval
Propranolol	2	Triptans	Unknown mechanism. Possible inhibition of triptan metabolism (monoamine oxidase-A) by propranolol resulting in enhanced pharmacologic effects and plasma concentrations.
Sotalol	2	Cisapride	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when cisapride is co-administered with sotalol.
Sotalol	2	H-1 Antagonists	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and H-1 antagonists are coadministered.
Sotalol	2	Iloperidone	Prolonged QT interval and cardiac arrhythmias are a potential when sotalol and iloperidone are used concomitantly.
Sotalol	2	Macrolides	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and macrolides are coadministered.
Sotalol	2	Mefloquine	Co-administration of mefloquine and sotalol may cause cardiovascular toxicity, including electrocardiographic abnormalities such as QT interval prolongation
Sotalol	2	Mibefradil	Co-administration of sotalol and mibefradil may cause cardiovascular toxicity.
Sotalol	2	Paliperidone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when paliperidone is co-administered with sotalol.
Sotalol	2	Propafenone	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered when sotalol and propafenone are coadministered.

Generic Name(s)	Significance Level	Interaction	Mechanism
Sotalol	2	Saquinavir	Coadministration of sotalol with saquinavir/ritonavir may be associated arrhythmias due to potential additive effects on prolongation of the QT interval.
Sotalol	2	Tricyclic Antidepressants	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when tricyclic antidepressants and sotalol are coadministered.
Thiazides (hydrochlorothiazide, chlorthalidone, bendroflumethazide)	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Thiazides (hydrochlorothiazide, chlorthalidone, bendroflumethazide)	2	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the beta-adrenergic blocking agents are listed in Tables 8 – 9. The boxed warnings for the beta-adrenergic blocking agents are listed in Tables 10 – 15.

Table 8. Adverse Drug Events (%) Reported with the Beta-Adrenergic Blocking Agents (Drugs A – M)[4-27]

Adverse Events	Acebutolol	Atenolol	Atenolol/ Chlorthalidone	Betaxolol	Bisoprolol	Bisoprolol/ HCTZ	Carvedilol	Labetalol	Metoprolol	Metoprolol/ HCTZ
Cardiovascular										
Angina	-	-	-	<2	-	-	1-6	-	-	-
Arrhythmia	-	-	-	<2	<1	<1	-	-	-	-
Arterial/vascular insufficiency	-	-	-	-	-	-	-	-	1	1
Bradycardia	1-10	1-10	1-10	6-8	<1	<1	2-10	<1	2-16	2-16
Cardiogenic shock	-	-	-	-	-	-	-	-	✔	✔
Cerebrovascular accident	-	-	-	-	-	-	≤4	-	-	-
Chest pain	2	1-10	1-10	2-7	1-2	1-2	-	-	1	1
Cold extremities	-	1-10	1-10	2	<1	<1	-	-	1	1
Congestive heart failure	1-10	1-10	1-10	<2	<1	<1	-	<1	1	1
Edema	2	1-10	1-10	≤2	<1	<1	5-6	≤2	-	-
Flushing	-	-	-	-	<1	<1	-	1	-	-
Heart block	✔	1-10	1-10	<2	-	-	≤4	<1	5	5
Hypertension	-	-	-	<2	-	-	≤4	-	-	-
Hypotension	1-10	1-10	1-10	<2	<1	1-10	9-20	1-5	1-27	1-27
Myocardial contractility impaired	-	-	-	-	-	<1	-	-	-	<1
Orthostatic hypotension	-	-	-	-	<1	1-10	-	-	-	1-10
Palpitations	✔	-	-	2	<1	<1	≤4	-	1	1
Peripheral circulation reduced	-	-	-	-	-	-	<1	-	-	-
Peripheral edema	-	-	-	-	-	-	1-7	-	1	1
Postural hypotension	-	-	-	-	-	-	≤4	-	-	-
Rhythm disturbance	-	-	-	-	<1	<1	-	-	-	-
Shortness of breath	-	-	-	-	-	-	-	-	✔	✔
Syncope	-	-	-	<2	<1	<1	3-8	<1	1	1
Ventricular arrhythmias	✔	-	-	-	-	-	-	-	-	-
Central Nervous System										
Abnormal dreams	2	-	-	<1	-	-	-	-	-	-
Anxiety	1-10	-	-	-	<1	<1	-	-	✔	✔
Concentration decreased	-	-	-	-	-	-	<1	-	-	-
Confusion	-	1-10	1-10	-	<1	<1	-	-	✔	✔
Depression	2	1-10	1-10	<1	<1	<1	1-10	-	5	5

Adverse Events	Acebutolol	Atenolol	Atenolol/ Chlorthalidone	Betaxolol	Bisoprolol	Bisoprolol/ HCTZ	Carvedilol	Labetalol	Metoprolol	Metoprolol/ HCTZ
Diaphoresis	-	-	-	<2	-	-	<1	-	-	-
Dizziness	6	1-10	1-10	-	<1	<1	2-32	1-20	2-10	2-10
Fatigue	11	1-10	1-10	3-10	6-8	6-8	4-24	1-11	1-10	1-10
Fever	-	-	-	<2	-	-	1-10	-	-	-
Hallucinations	-	<1	<1	<2	<1	<1	-	-	✔	✔
Headache	6	1-10	1-10	-	<1	<1	5-8	2	✔	✔
Hyper/hypoesthesia	1-10	-	-	-	1-2	1-2	1-10	-	-	-
Insomnia	3	1-10	1-10	1-5	2-3	2-3	1-10	-	✔	✔
Lethargy	-	1-10	1-10	3	-	-	-	-	-	-
Malaise	-	-	-	<2	<1	<1	1-10	-	-	-
Memory loss	-	-	-	<2	<1	<1	<1	-	✔	✔
Mental impairment	-	1-10	1-10	-	-	-	-	-	-	-
Nervousness	-	-	-	-	<1	<1	<1	-	✔	✔
Nightmares/vivid dreams	-	1-10	1-10	-	-	-	<1	-	✔	✔
Paresthesia	-	-	<1	-	<1	<1	-	-	✔	✔
Psychosis	-	<1	<1	-	-	-	-	-	-	-
Sleep disturbance	-	-	-	-	<1	<1	-	-	✔	✔
Somnolence	-	-	-	-	<1	<1	1-10	3	✔	✔
Vertigo	-	-	-	-	<1	<1	1-10	1-2	✔	✔
Dermatologic										
Acne	-	-	-	-	<1	<1	-	-	-	-
Alopecia	-	<1	<1	<2	<1	<1	<1	<1	✔	<1
Dermatitis	-	-	-	-	<1	-	-	-	-	-
Eczema	-	-	-	-	<1	-	-	-	-	-
Erythema multiforme	-	-	-	-	-	<1	<1	-	-	<1
Exfoliative dermatitis	-	-	-	-	-	<1	<1	-	-	<1
Photosensitivity	-	-	1-10	-	-	1-10	<1	-	✔	1-10
Pruritus	1-10	-	-	-	<1	<1	<1	1	5	5
Psoriasiform rash	-	<1	<1	-	<1	<1	-	<1	-	-
Psoriasis (exacerbated)	-	-	-	-	<1	<1	-	-	✔	✔
Purpura	-	-	<1	-	<1	<1	-	-	-	-
Rash	2	-	<1	1	<1	<1	<1	1	5	5
Scalp tingling	-	-	-	-	-	-	-	≤7	-	-
Stevens-Johnson syndrome	-	-	-	-	-	<1	<1	-	-	<1
Sweating, excessive	-	-	-	-	-	-	-	-	✔	✔
Systemic lupus erythematosus	✔	-	-	-	-	-	-	-	-	-
Toxic epidermal necrolysis	-	-	-	-	-	<1	<1	-	-	<1

Adverse Events	Acebutolol	Atenolol	Atenolol/ Chlorthalidone	Betaxolol	Bisoprolol	Bisoprolol/ HCTZ	Carvedilol	Labetalol	Metoprolol	Metoprolol/ HCTZ
Urticaria	-	-	<1	-	-	-	-	<1	✔	✔
Endocrine and Metabolic										
Diabetes (exacerbated)	-	-	-	<2	-	-	1-10	-	✔	✔
Glycosuria	-	-	<1	-	-	-	-	-	-	-
Gout	-	-	<1	-	<1	<1	1-10	-	-	-
Libido decreased	-	-	-	-	-	-	-	-	✔	✔
Gastrointestinal										
Abdominal pain	1-10	-	-	-	<1	<1	1-10	-	✔	✔
Anorexia	✔	-	1-10	<2	-	1-10	-	-	-	1-10
Constipation	4	1-10	1-10	<2	<1	<1	-	-	1	1
Diarrhea	4	1-10	1-10	2	3-4	3-4	-	-	5	5
Dyspepsia	4	-	-	4-5	<1	<1	-	≤4	-	-
Epigastric distress	-	-	1-10	-	-	1-10	-	-	-	1-10
Flatulence	3	-	-	-	-	-	-	-	1	1
Gastritis/gastric irritation	-	-	-	-	<1	<1	-	-	-	-
Gastrointestinal hemorrhage	-	-	-	-	-	-	<1	-	-	-
Heartburn	-	-	-	-	-	-	-	-	1	1
Melena	-	-	-	-	-	-	1-10	-	-	-
Nausea	4	1-10	1-10	2-6	2	2	2-9	≤19	1	1
Pancreatitis	-	-	<1	-	-	-	<1	-	-	<1
Peptic ulcer	-	-	-	-	<1	<1	-	-	-	-
Periodontitis	-	-	-	-	-	-	1-10	-	-	-
Retroperitoneal fibrosis	-	-	-	-	-	-	-	-	✔	✔
Taste disorder	-	-	-	<2	<1	<1	-	1	✔	✔
Vomiting	1-10	-	<1	<2	1-2	1-2	1-6	≤3	✔	✔
Weight gain	-	-	-	<2	<1	<1	10-12	-	✔	✔
Xerostomia	✔	-	-	<2	<1	<1	<1	-	-	-
Genitourinary										
Cystitis	-	-	-	<2	<1	<1	-	-	-	-
Diabetes insipidus	-	-	-	-	-	-	-	<1	-	-
Dysuria	1-10	-	-	<2	-	-	-	-	-	-
Ejaculatory failure	-	-	-	-	-	-	-	≤5	-	-
Hematuria	-	-	-	-	-	-	1-10	-	-	-
Impotence	1-10	1-10	1-10	-	<1	<1	1-10	1-4	✔	✔
Libido decreased	-	-	-	<2	<1	<1	<1	-	-	-
Micturition (frequency)	3	-	-	-	-	-	-	-	-	-
Nocturia	1-10	-	-	-	-	-	-	-	-	-

Adverse Events	Acebutolol	Atenolol	Atenolol/ Chlorthalidone	Betaxolol	Bisoprolol	Bisoprolol/ HCTZ	Carvedilol	Labetalol	Metoprolol	Metoprolol/ HCTZ
Polyuria	-	-	<1	-	<1	<1	-	-	-	-
Urinary incontinence	-	-	-	-	-	-	<1	-	-	-
Urinary retention	✔	-	-	-	-	-	-	<1	-	-
Hematologic										
Agranulocytosis	-	-	<1	-	-	-	<1	-	✔	<1
Anemia (aplastic/hemolytic)	-	-	<1	<2	-	-	1-10	-	-	<1
Claudication	-	-	-	-	-	-	-	-	✔	✔
Leukopenia	-	-	<1	-	<1	<1	<1	-	-	<1
Pancytopenia	-	-	-	-	-	-	<1	-	-	-
Prothrombin decreased	-	-	-	-	-	-	1-10	-	-	-
Purpura	-	-	<1	<2	-	-	1-10	-	-	-
Thrombocytopenia	-	<1	<1	<2	<1	<1	1-10	-	✔	<1
Hepatic										
Cholestatic jaundice	-	-	-	-	-	-	<1	<1	-	-
Hepatic impairment	✔	-	<1	-	-	-	<1	<1	-	<1
Hepatitis	-	-	-	-	-	-	-	<1	✔	✔
Increase liver enzymes	-	<1	<1	-	-	-	-	-	-	-
Transaminases increase	✔	-	-	<2	<1	<1	1-10	4	✔	✔
Laboratory Test Abnormalities										
Alkaline phosphatase increased	✔	-	-	-	-	-	-	-	✔	✔
Hypercalcemia	-	-	<1	-	-	-	<1	-	-	<1
Hypercholesterolemia	-	-	-	<2	-	-	1-4	-	-	-
Hyperglycemia	-	-	<1	<2	-	-	-	-	-	-
Hyperkalemia	-	-	-	<2	<1	<1	1-10	-	-	-
Hypernatremia	-	-	<1	-	-	-	-	-	-	-
Hyperphosphatemia	-	-	-	-	-	-	3-6	-	-	-
Hypertriglyceridemia	-	-	-	-	<1	<1	1	-	-	-
Hyperuricemia	-	-	<1	<2	<1	<1	1-10	-	-	-
Hypervolemia	-	-	-	-	-	-	≤4	-	-	-
Hypoglycemia	-	-	-	<2	<1	<1	1-10	-	-	-
Hyponatremia	-	-	<1	-	-	-	1-10	-	-	-
Hypokalemia	-	-	1-10	<2	-	-	1-10	-	-	1-10
Lactate dehydrogenase increased	-	-	-	-	-	-	-	-	✔	✔
Musculoskeletal										
Arthralgia	-	-	-	3-5	1-10	1-10	1-6	-	✔	✔
Arthritis	-	-	-	-	-	-	-	-	✔	✔
Asthenia	-	-	-	-	≤2	≤2	-	-	-	-

Adverse Events	Acebutolol	Atenolol	Atenolol/ Chlorthalidone	Betaxolol	Bisoprolol	Bisoprolol/ HCTZ	Carvedilol	Labetalol	Metoprolol	Metoprolol/ HCTZ
Back pain	1-10	-	-	-	<1	<1	2-7	-	-	-
Joint pain	1-10	-	-	-	<1	<1	-	-	-	-
Muscle cramps	-	-	<1	<2	<1	<1	1-10	-	-	-
Muscle pain	-	-	-	-	<1	<1	-	-	✔	✔
Muscle spasm	-	-	<1	-	-	-	-	-	-	-
Myalgia	2	-	-	-	-	-	-	-	-	-
Neuralgia	-	-	-	<2	-	-	<1	-	-	-
Paresthesia	-	-	-	-	-	-	-	≤5	-	-
Peripheral ischemia	✔	-	-	-	-	-	-	-	-	-
Restlessness	-	-	<1	-	<1	<1	-	-	-	-
Tremor	-	-	-	<2	<1	<1	-	-	-	-
Toxic myopathy	-	-	-	-	-	-	-	<1	-	-
Twitching	-	-	-	<2	<1	<1	-	-	-	-
Weakness	-	-	<1	-	-	-	7-11	1	-	-
Renal										
Blood urea nitrogen increased	-	-	-	-	<1	<1	≤6	≤8	-	-
Creatinine increase	-	-	-	-	<1	<1	1-10	-	-	-
Glycosuria	-	-	-	-	-	-	1-10	-	-	-
Hematuria	-	-	-	-	1-10	1-10	-	-	-	-
Interstitial nephritis	-	-	-	-	-	-	<1	-	-	<1
Renal colic	-	-	-	-	<1	<1	-	-	-	-
Renal failure/dysfunction	-	-	-	-	-	-	1-10	-	-	<1
Respiratory										
Asthma	-	-	-	-	<1	<1	<1	-	-	-
Bronchitis	-	-	-	-	<1	<1	-	-	-	-
Bronchospasm	-	-	-	-	<1	<1	<1	<1	1	1
Cough	1	-	-	<2	<1	<1	5-8	-	-	-
Dyspnea	4	<1	<1	2	1-2	1-2	>3	2	1-3	1-3
Eosinophilic pneumonitis	-	-	-	-	-	-	<1	-	-	<1
Interstitial pneumonitis	-	-	-	-	-	-	<1	-	-	-
Nasal congestion	-	-	-	-	-	-	1	1-6	-	-
Nasopharyngitis	-	-	-	-	-	-	4	-	-	-
Pharyngitis	1-10	-	-	2	<1	<1	-	-	-	-
Pleurisy	✔	-	-	-	-	-	-	-	-	-
Pneumonitis	✔	-	-	-	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	-	>3	-	-	-
Pulmonary granulomas	✔	-	-	-	-	-	-	-	-	-

Adverse Events	Acebutolol	Atenolol	Atenolol/ Chlorthalidone	Betaxolol	Bisoprolol	Bisoprolol/ HCTZ	Carvedilol	Labetalol	Metoprolol	Metoprolol/ HCTZ
Respiratory failure/distress	-	-	-	-	-	-	<1	-	-	<1
Rhinitis	2	-	-	-	3-4	3-4	2	-	✔	✔
Sinus congestion	-	-	-	-	-	-	1	-	-	-
Sinusitis	-	-	-	-	2	2	-	-	-	-
Upper respiratory infection	-	-	-	-	5	5	-	-	-	-
Wheezing	1-10	<1	<1	-	-	-	-	-	1	1
Special Senses										-
Abnormal/blurred vision	2	-	-	-	-	-	1-5	1	✔	✔
Blepharitis	-	-	-	<2	-	-	-	-	-	-
Cataract	-	-	-	<2	-	-	-	-	-	-
Conjunctivitis	1-10	-	-	-	-	-	-	-	-	-
Dry eyes	1-10	-	-	-	-	-	-	-	✔	✔
Eye pain	1-10	-	-	-	<1	<1	-	-	-	-
Hearing decreased	-	-	-	<2	<1	<1	<1	-	-	-
Lacrimation, abnormal	-	-	-	-	<1	<1	-	-	-	-
Tinnitus	-	-	-	<2	<1	<1	<1	-	-	-
Visual disturbances	-	-	-	<2	<1	<1	-	-	✔	✔
Other										
Allergy/allergic reaction	-	-	-	-	-	-	1-10	-	-	<1
Anaphylactoid reaction	-	-	-	-	-	-	<1	<1	-	-
Angioedema	-	-	-	-	-	-	-	<1	-	-
Cholecystitis	-	-	<1	-	-	-	-	-	-	-
Cutaneous vasculitis	-	-	<1	-	<1	<1	-	-	-	-
Diaphoresis	-	-	-	-	-	-	-	≤4	-	-
Gangrene	-	-	-	-	-	-	-	-	✔	✔
Hypersensitivity	-	-	-	-	-	-	-	<1	-	-
Lupus syndrome	✔	<1	<1	-	-	-	-	<1	-	-
Metabolic acidosis	-	-	-	<2	-	-	-	-	-	-
Necrotizing angiitis	-	-	<1	-	-	-	-	-	-	-
Peyronie's disease	-	<1	<1	<2	<1	<1	-	<1	<1	<1
Positive antinuclear antibody test	-	<1	<1	5	<1	<1	1-10	<1	-	-
Tinnitus	-	-	-	-	-	-	-	-	✔	✔

✔ Percent not specified
- Event not reported

Table 9. Adverse Drug Events (%) Reported with the Beta-Adrenergic Blocking Agents (Drugs N – T)[4-27]

Adverse Events	Nadolol	Nadolol/ Bendroflumethiazide	Nebivolol	Penbutolol	Pindolol	Propranolol	Propranolol/ HCTZ	Sotalol	Timolol
Cardiovascular									
Angina	-	-	-	-	-	✔	✔	-	✔
Arrhythmia	<1	<1	-	1-10	-	-	-	5	✔
Arterial/vascular insufficiency	-	-	<1	-	-	✔	✔	-	-
Atrioventricular nodal disturbances	-	-	-	-	-	✔	✔	-	-
Bradycardia	1-10	1-10	≤1	<1	≤2	6	6	13-16	1-10
Cardiac failure/arrest	-	-	-	-	-	-	-	-	✔
Cardiogenic shock	-	-	-	-	-	✔	✔	-	-
Chest pain	<1	<1	≤1	-	3	2-4	2-4	3-16	-
Cold extremities	1-10	1-10	-	<1	≤2	✔	✔	<1	✔
Congestive heart failure	1-10	1-10	-	1-10	<1	✔	✔	5	-
Edema	1-10	1-10	-	<1	6	2	2	8	✔
Electrocardiogram abnormal	-	-	-	-	-	-	-	7	-
Heart block	-	-	-	<1	≤2	-	-	-	✔
Hypotension	-	-	-	<1	≤2	✔	1-10	6	✔
Myocardial contractility impaired	-	-	-	-	-	✔	<1	-	-
Myocardial ischemia	-	-	<1	-	-	-	-	-	-
Orthostatic hypotension	<1	<1	-	-	-	-	1-10	-	-
Palpitations	1-10	1-10	-	-	≤1	-	-	14	✔
Peripheral circulation reduced	1-10	1-10	-	-	-	-	-	3	-
Peripheral edema	-	-	1	-	-	-	-	-	-
Syncope	-	-	<1	-	≤2	✔	✔	5	-
Tachycardia	-	-	-	-	≤2	-	-	-	-
Torsade de pointes	-	-	-	-	-	-	-	1-4	-
Thrombosis, mesenteric arterial	-	-	-	-	-	✔	✔	-	-
Central Nervous System									
Abnormal dreams	-	-	-	-	-	3	3	-	-
Amnesia	-	-	-	-	-	✔	✔	-	-
Anxiety	-	-	-	-	-	-	-	4	✔
Catatonia	-	-	-	-	-	✔	✔	-	-
Cerebral ischemia	-	-	-	-	-	-	-	-	✔
Cerebral vascular accident	-	-	-	-	-	-	-	-	✔
Cognitive dysfunction	-	-	-	-	-	✔	✔	-	-
Confusion	<1	<1	-	<1	-	✔	✔	6	✔
Depression	1-10	1-10	-	1-10	-	1-3	1-3	4	✔
Disorientation	-	✔	-	-	-	-	-	-	✔

Adverse Events	Nadolol	Nadolol/ Bendroflumethiazide	Nebivolol	Penbutolol	Pindolol	Propranolol	Propranolol/ HCTZ	Sotalol	Timolol
Dizziness	-	-	2-4	1-10	9	2-11	2-11	20	1-10
Drowsiness	>10	>10	-	-	-	2	2	-	-
Emotional lability	-	-	-	-	-	✔	✔	<1	-
Fatigue	-	✔	2-5	1-10	8	3-17	3-17	20	1-10
Hallucinations	<1	<1	-	-	<1	✔	✔	-	✔
Headache	<1	<1	6-9	1-10	-	1-9	1-9	8	-
Insomnia	>10	>10	1	<1	10	3-8	3-8	-	✔
Lethargy	-	-	-	<1	-	4	4	-	-
Lightheadedness	-	-	-	-	-	✔	✔	12	-
Memory loss	-	-	-	-	-	-	-	-	✔
Nervousness	<1	<1	-	-	7	2	2	-	✔
Nightmares/vivid dreams	-	✔	-	<1	5	✔	✔	-	✔
Psychosis	-	-	-	-	-	✔	✔	-	-
Sleep disturbance	-	-	-	-	-	-	-	8	-
Somnolence	-	✔	-	-	-	✔	✔	-	✔
Vertigo	-	-	<1	-	-	✔	✔	<1	-
Dermatologic									
Alopecia	-	-	-	-	-	✔	<1	<1	✔
Cutaneous ulcers	-	-	-	-	-	✔	✔	-	-
Dermatitis	-	-	✔	-	-	✔	✔	-	-
Eczematous eruptions	-	-	-	-	-	✔	✔	-	-
Erythema multiforme	-	✔	-	-	-	✔	<1	-	-
Exfoliative dermatitis	-	✔	-	-	-	✔	<1	-	-
Hyperkeratosis	-	-	-	-	-	✔	✔	-	-
Nail changes	-	-	-	-	-	✔	✔	-	-
Oculomucocutaneous reactions	-	-	-	-	-	✔	✔	-	-
Photosensitivity	-	✔	-	-	-	-	1-10	<1	-
Pruritus	-	-	<1	-	1	✔	✔	<1	-
Pseudo pemphigoid	-	-	-	-	-	-	-	-	✔
Psoriasiform rash	-	-	-	-	-	✔	✔	-	✔
Psoriasis (exacerbated)	-	✔	<1	-	-	-	-	-	✔
Purpura	-	✔	-	-	-	-	-	-	-
Rash	-	-	≤1	-	-	0-2	0-2	5	✔
Red crusted skin	-	-	-	-	-	-	-	<1	-
Skin necrosis after extravasation	-	-	-	-	-	-	-	<1	-
Stevens-Johnson syndrome	-	-	-	-	-	✔	<1	-	-
Sweating, excessive	-	-	-	-	≤2	2	2	<1	-

Adverse Events	Nadolol	Nadolol/ Bendroflumethiazide	Nebivolol	Penbutolol	Pindolol	Propranolol	Propranolol/ HCTZ	Sotalol	Timolol
Toxic epidermal necrolysis	-	✔	-	-	-	✔	<1	-	-
Ulcers	-	-	-	-	-	✔	✔	-	-
Urticaria	-	-	<1	-	-	✔	✔	5	✔
Endocrine and Metabolic									
Diabetes (exacerbated)	-	✔	-	-	-	-	-	-	-
Hypoglycemia masked	-	-	-	-	-	-	-	-	✔
Libido decreased	-	-	-	-	-	-	-	-	✔
Gastrointestinal									
Abdominal pain	-	-	1-10	-	-	1	1	-	-
Anorexia	-	✔	-	-	-	✔	1-10	-	✔
Constipation	1-10	1-10	-	-	-	0-2	0-2	-	-
Cramping	-	✔	-	-	-	✔	✔	-	-
Diarrhea	1-10	1-10	2-3	1-10	≤2	2-7	2-7	7	✔
Dry mouth	-	-	-	-	-	-	-	-	✔
Dyspepsia	-	✔	-	1-10	-	1-7	1-7	-	✔
Epigastric distress	-	-	-	-	-	-	1-10	-	-
Flatulence	-	-	-	-	-	4	4	2	-
Ischemic colitis	-	-	-	<1	-	✔	✔	-	-
Melena	-	✔	-	-	-	-	-	-	-
Nausea	1-10	1-10	1-3	1-10	5	1-6	1-6	10	✔
Pancreatitis	-	-	-	-	-	-	<1	-	-
Periodontitis	-	✔	-	-	-	-	-	-	-
Retroperitoneal fibrosis	-	-	-	-	-	-	-	-	✔
Stomach discomfort	1-10	1-10	-	-	-	✔	✔	3-6	-
Taste disorder	-	✔	-	-	-	-	-	-	-
Vomiting	1-10	1-10	<1	-	≤2	✔	✔	10	-
Weight gain	-	-	-	-	≤2	-	-	-	-
Genitourinary									
Impotence	-	-	<1	-	≤2	1	1	2	✔
Interstitial nephritis	-	-	-	-	-	✔	✔	-	-
Micturition (frequency)	-	-	-	-	-	1	1	-	-
Oliguria	-	-	-	-	-	✔	✔	-	-
Polyuria	-	-	-	-	≤2	-	-	-	-
Proteinuria	-	-	-	-	-	✔	✔	-	-
Sexual ability decreased	>10	>10	-	-	-	-	-	3	-
Hematologic									
Agranulocytosis	-	-	-	-	-	✔	<1	-	-

Adverse Events	Nadolol	Nadolol/ Bendroflumethiazide	Nebivolol	Penbutolol	Pindolol	Propranolol	Propranolol/ HCTZ	Sotalol	Timolol
Anemia (aplastic/hemolytic)	-	✔	-	-	-	-	<1	-	-
Bleeding	-	-	-	-	-	-	-	2	-
Claudication	-	-	-	-	-	-	-	-	✔
Eosinophilia	-	-	-	-	-	-	-	<1	-
Leukopenia	<1	<1	-	-	-	-	<1	<1	-
Prothrombin decreased	-	✔	-	-	-	-	-	-	-
Purpura	-	-	-	<1	-	✔	✔	-	-
Thrombocytopenia	<1	<1	1-10	<1	-	✔	✔	<1	-
Hepatic									
Cholestatic jaundice	-	✔	-	-	-	-	-	-	-
Hepatic impairment	-	-	-	-	-	-	<1	-	-
Increase liver enzymes	-	-	<1	-	7	-	-	-	-
Transaminases increase	-	-	-	-	-	✔	✔	<1	-
Laboratory Test Abnormalities									
Alkaline phosphatase increased	-	-	-	-	<1	✔	✔	-	-
Electrolyte imbalance	-	✔	-	-	-	-	-	-	-
Hypercalcemia	-	-	-	-	-	-	<1	-	-
Hypercholesterolemia	-	-	1-10	-	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	✔	✔	-	-
Hyperkalemia	-	-	-	-	-	✔	✔	-	-
Hyperlipidemia	-	-	-	-	-	✔	✔	<1	-
Hyperphosphatemia	-	✔	-	-	-	-	-	-	-
Hypertriglyceridemia	-	✔	-	-	-	-	-	-	-
Hyperuricemia	-	-	1-10	-	<1	-	-	-	-
Hypoglycemia	-	-	-	<1	-	✔	✔	-	-
Hypokalemia	-	-	-	-	-	-	1-10	-	-
Lactate dehydrogenase increased	-	-	-	-	<1	-	-	-	-
Musculoskeletal									
Arthralgia	-	-	-	1-10	7	1	1	-	-
Arthropathy	-	-	-	-	-	✔	✔	-	-
Back pain	-	-	-	-	-	-	-	3	-
Carpal Tunnel syndrome	-	-	-	-	-	✔	✔	-	-
Extremity pain	-	-	-	-	-	-	-	7	-
Muscle cramps	-	✔	-	-	3	-	-	-	-
Muscle pain	-	-	-	-	10	-	-	-	-
Myalgia	-	-	-	-	-	1	1	<1	-
Myasthenia gravis exacerbated	-	-	-	-	-	-	-	-	✔

Adverse Events	Nadolol	Nadolol/ Bendroflumethiazide	Nebivolol	Penbutolol	Pindolol	Propranolol	Propranolol/ HCTZ	Sotalol	Timolol
Myotonus	-	-	-	-	-	✔	✔	-	-
Neuralgia	-	✔	-	-	-	-	-	-	-
Paralysis	-	-	-	-	-	-	-	<1	-
Paresthesia	-	-	1-10	-	3	✔	✔	4	✔
Polyarthritis	-	-	-	-	-	✔	✔	-	-
Tremor	-	✔	-	-	-	-	-	-	-
Weakness	-	✔	1-10	-	4	1	1	13	-
Renal									
Blood urea nitrogen increase	-	-	1-10	-	-	✔	✔	-	-
Interstitial nephritis	-	-	-	-	-	-	<1	-	-
Renal failure	-	-	<1	-	-	-	<1	-	-
Respiratory									
Asthma	-	-	-	-	-	-	-	2	-
Bronchospasm	1-10	1-10	<1	<1	-	✔	✔	-	✔
Cough	-	-	-	<1	-	1	1	-	✔
Dyspnea	<1	<1	≤1	-	5	1-6	1-6	21	1-10
Eosinophilic pneumonitis	-	-	-	-	-	-	<1	-	-
Laryngospasm	-	-	-	-	-	✔	✔	-	-
Nasal congestion	-	-	-	-	-	-	-	-	✔
Nasopharyngitis	-	✔	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	-	✔	✔	-	-
Pulmonary edema	-	-	<1	-	-	✔	✔	<1	✔
Respiratory failure	-	-	-	-	-	✔	<1	-	✔
Rhinitis	-	-	-	-	-	1	1	-	-
Upper respiratory infection	-	-	-	-	-	5	5	5-8	-
Wheezing	-	✔	-	-	≤2	✔	✔	-	-
Special Senses									
Abnormal/blurred vision	-	-	-	-	-	3	3	-	-
Burning	-	-	-	-	≤2	-	-	-	-
Corneal sensitivity decrease	-	-	-	-	-	-	-	-	✔
Cystoid macular edema	-	-	-	-	-	-	-	-	✔
Diplopia	-	-	-	-	-	-	-	-	✔
Dry eyes	-	-	-	-	-	-	-	-	✔
Eye discomfort	-	-	-	-	≤2	-	-	-	-
Hyperemia of conjunctiva	-	-	-	-	-	✔	✔	-	-
Keratitis	-	-	-	-	-	-	-	-	✔
Lacrimation abnormal	-	✔	-	-	-	-	-	-	-

Adverse Events	Nadolol	Nadolol/ Bendroflumethiazide	Nebivolol	Penbutolol	Pindolol	Propranolol	Propranolol/ HCTZ	Sotalol	Timolol
Mydriasis	-	-	-	-	-	✔	✔	-	-
Ocular discharge	-	-	-	-	-	-	-	-	✔
Ocular pain	-	-	-	-	-	-	-	-	✔
Ptosis	-	-	-	-	-	-	-	-	✔
Refractive changes	-	-	-	-	-	-	-	-	✔
Tinnitus	-	-	-	-	-	-	-	-	✔
Visual disturbances	-	-	-	-	≤2	✔	✔	5	✔
Xerophthalmia	-	-	-	-	-	✔	✔	-	-
Other									
Allergy	-	-	-	-	-	-	<1	-	✔
Anaphylactoid reaction	-	-	-	-	-	✔	✔	-	-
Angioedema	-	✔	<1	-	-	-	-	-	✔
Hypersensitivity	-	-	<1	-	-	-	-	-	-
Hypervolemia	-	✔	-	-	-	-	-	-	-
Lupus syndrome	-	✔	-	-	-	✔	✔	-	✔
Mesenteric arterial thrombosis	-	-	-	<1	-	-	-	-	-
Peyronie's disease	-	-	-	-	-	✔	✔	-	✔

✔ Percent not specified
\- Event not reported

Table 10. Boxed Warning for Atenolol[4]

WARNING
Advise patients with coronary artery disease who are being treated with atenolol against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction (MI) and ventricular arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with β-blockers. The last 2 complications may occur with or without preceding exacerbation of the angina pectoris. As with other β-blockers, when discontinuation of atenolol is planned, observe the patient carefully and advise the patient to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that atenolol be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue atenolol therapy abruptly, even in patients treated only for hypertension.

Table 11. Boxed Warning for Metoprolol[4]

WARNING
Ischemic heart disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and carefully monitor the patient. If angina markedly worsens or acute coronary insufficiency develops, reinstate metoprolol administration promptly, at least temporarily, and take other measures appropriate for the management of unstable angina. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol therapy abruptly, even in patients treated only for hypertension.

Table 12. Boxed Warning for Nadolol[4]

WARNING
Exacerbation of ischemic heart disease following abrupt withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from β-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of one to two weeks and carefully monitor the patient. If angina markedly worsens or acute coronary insufficiency develops, reinstitute nadolol administration promptly, at least temporarily, and take other measures appropriate for the management of unstable angina. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly, even in patients treated only for hypertension.

Table 13. Boxed Warning for Propranolol[4]

WARNING
Angina pectoris: There have been reports of exacerbation of angina and, in some cases, myocardial infarction (MI), following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without a health care provider's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it is usually advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Because coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Table 14. Boxed Warning for Sotalol[4]

WARNING
To minimize the risk of induced arrhythmia, place patients initiated or reinitiated on sotalol AF or sotalol for a minimum of 3 days (on their maintenance dose) in a facility that can provide cardiac resuscitation, continuous electrocardiographic (ECG) monitoring, and calculations of creatinine clearance. Calculate creatinine clearance prior to dosing. Do not substitute sotalol for sotalol AF because of significant differences in labeling (i.e., patient package insert, dosing administration, safety information).

Table 15. Boxed Warning for Timolol[4]

WARNING
Exacerbation of ischemic heart disease following abrupt withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from β-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of one to two weeks and carefully monitor the patient. If angina markedly worsens or acute coronary insufficiency develops, reinstitute timolol administration promptly, at least temporarily, and take other measures appropriate for the management of unstable angina. Warn patients against interruption of discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol therapy abruptly, even in patients treated only for hypertension.

VII. Dosing and Administration

The usual dosing regimens for the beta-adrenergic blocking agents are listed in Table 16.

Table 16. Usual Dosing Regimens for the Beta-Adrenergic Blocking Agents[4-27]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acebutolol	Hypertension: Initial: 400 mg/day, twice-daily dosing may be required for adequate control; maintenance: 200 to 1,200 mg/day in two divided doses; maximum: 1,200 mg/day Ventricular Arrhythmias: Initial: 200 mg twice daily; maintenance: gradual increase until optimal response, usually 600 to 1,200 mg/day; maximum: 1,200 mg/day	Safety and efficacy in children have not been established.	Capsule: 200 mg 400 mg
Atenolol	Acute Myocardial Infarction: 50 mg twice daily, or 100 mg once daily for 6 to 9 days or until hospital discharge Angina Pectoris: Initial: 50 mg once daily; maintenance: if optimal response not achieved after 1 week, increase to 100 mg daily; maximum: 200 mg/daily	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Initial: 50 mg once daily; maintenance: if optimal response not achieved, increase dose to 100 mg once daily; maximum: 100 mg/day		
Atenolol and chlorthalidone	Hypertension: Initial: 50/25 mg once daily; maintenance: if optimum response is not achieved after 1-2 weeks, may increase to 100/25 mg once daily	Safety and efficacy in children have not been established.	Tablet: 50 mg-25 mg 100 mg-25 mg
Betaxolol	Hypertension: Initial: 10 mg once daily; maintenance: if optimal response not seen after 7 to 14 days, may increase the dose to 20 mg daily; maximum: 40 mg/day	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg
Bisoprolol	Hypertension: Initial: 2.5 to 5 mg once daily; maintenance: if optimal control is not achieved, dose may be increased to 10 mg daily and again to 20 mg daily if needed; maximum: 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Bisoprolol and hydrochlorothiazide	Hypertension: Initial: 2.5/6.25 mg once daily; maintenance: may titrate dose every 7 to 14 days up to a maximum of 20/12.5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 2.5 mg-6.25 mg 5 mg-6.25 mg 10 mg-6.25 mg
Carvedilol	Heart Failure: Capsule ER: initial, 10 mg once daily; maintenance: if tolerated, double the dose at intervals of >14 days as needed up to a maximum of 80 mg once daily Tablet IR: initial, 3.125 mg twice daily; maintenance: if tolerated, double the dose at intervals of >14 days as needed up to 50 mg twice daily; maximum: 25 mg twice daily (patients ≤85 kg) or 50 mg twice daily (patients >85 kg) Hypertension: Capsule ER: initial, 20 mg once daily; maintenance: if tolerated, double the dose every 7 to 14 days as needed	Efficacy in children have not been established.	Capsule (ER): 10 mg 20 mg 40 mg 80 mg Tablet (IR): 3.125 mg 6.25 mg 12.5 mg 25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	up to a maximum of 80 mg once daily Tablet IR: initial, 6.25 mg twice daily; maintenance: if tolerated, double the dose every 7 to 14 days as needed up to a maximum of 25 mg twice daily Post-Myocardial Infarction: Capsule ER: initial, 10 to 20 mg once daily; maintenance: if tolerated, double the dose every 3 to 10 days as needed up to a maximum of 80 mg once daily Tablet IR: initial, 6.25 mg twice daily; maintenance: if tolerated, double the dose every 3 to 10 days as needed up to a maximum of 25 mg twice daily		
Labetalol	Hypertension: Initial: 100 mg twice daily; maintenance: titrate by increments of 100 mg twice daily every 2 to 3 days, usual dose is 200 to 400 mg twice daily; larger doses may be administered three times daily to improve tolerability; maximum: doses of 1,200 to 2,400 mg daily have been used	Safety and efficacy in children have not been established.	Injection: 5 mg/ml Tablet: 100 mg 200 mg 300 mg
Metoprolol	Angina Pectoris: Tablet IR: initial, 100 mg/day in 2 divided doses; maintenance: gradually increase dose in weekly intervals up to a maximum of 400 mg/day; usual dose is 100 to 400 mg/day Tablet ER: initial, 100 mg once daily; maintenance: gradually increase dose in weekly intervals up to a maximum of 400 mg/day Heart Failure: Tablet ER (NYHA Class II): initial, 25 mg/day, double the dose every 2 weeks up to 200 mg/day or highest dose tolerated	Children ≥6 years of age: Hypertension (Tablet ER): Initial: 1 mg/kg once daily (max: 50 mg once daily); maintenance: adjust dose to optimal response up to 2 mg/kg or 200 mg/day; maximum: 2 mg/kg daily (max: 200 mg/day)	Injection: 5 mg/5 ml Tablet (IR): 25 mg 50 mg 100 mg Tablet (ER): 25 mg 50 mg 100 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet ER (more severe heart failure): initial, 12.5 mg/day, double the dose every 2 weeks up to 200 mg/day or highest dose tolerated Hypertension: Tablet IR: initial, 50 to 100 mg/day in single or divided doses; maintenance: gradually increase dose in weekly intervals up to a maximum of 450 mg/day; usual dose is 100 to 450 mg/day Tablet ER: initial, 25 to 100 mg once daily; maintenance: gradually increase dose in weekly intervals up to 400 mg/day Post-Myocardial Infarction: Tablet IR: 100 mg twice daily; maintenance: 100 mg twice daily for at least 3 months		
Metoprolol and hydrochlorothiazide	Hypertension: Initial: 100/25 mg/day in single or divided doses; maintenance: may titrate dose gradually until desired effect is achieved; usual dose of metoprolol is 100 to 450 mg/day, and of hydrochlorothiazide, 12.5 to 50 mg/day; may be administered in single or divided doses	Safety and efficacy in children have not been established.	Tablet: 50 mg-25 mg 100 mg-25 mg 100 mg-50 mg
Nadolol	Angina Pectoris: Initial: 40 mg once daily; maintenance: increase dose by 40 to 80 mg every 3 to 7 days until optimal response up to a maximum of 240 mg daily Hypertension: Initial: 40 mg once daily; maintenance: increase dose gradually by 40 to 80 mg increments every 7-21 days until optimal response up to a maximum of 320 mg daily	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg 80 mg
Nadolol and bendroflumethiazide	Hypertension: Initial: 40/5 mg once daily; maintenance: if desired effect is not achieved, may increase	Safety and efficacy in children have not been established.	Tablet: 40 mg-5 mg 80 mg-5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	dose to 80/5 mg once daily		
Nebivolol	Hypertension: Initial: 5 mg once daily; maintenance: increase in 2 week intervals until optimal response or a maximum of 40 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg
Penbutolol	Hypertension: Initial: 20 mg once daily; maintenance: 20 mg once daily; usual dose 10 to 40 mg once daily; maximum: 80 mg/day	Safety and efficacy in children have not been established.	Tablet: 20 mg
Pindolol	Hypertension: Initial: 5 mg twice daily; maintenance: after 3 to 4 weeks, may be increase by 10 mg/day increments as needed up to a maximum of 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Propranolol	Angina Pectoris: ER (Inderal LA®): initial, 80 mg once daily; maintenance: may gradually increase dose in 3 to 7 days increments up to 160 mg once daily or higher; usual dose is 160 mg daily; maximum: 320 mg/day IR: maintenance, 80 to 320 mg/day administered in two, three or four divided doses; maximum: 320 mg/day Atrial Fibrillation: IR: maintenance, 10 to 30 mg in three to four divided doses before meals and at bedtime Essential Tremor: IR: initial, 40 mg twice daily; maintenance: usual dose is 120 mg/day; maximum: 320 mg/day Hypertension: ER (Inderal LA®): initial, 80 mg once daily; maintenance: may titrate dose up to 120 mg daily or higher; usual dose is 120 to 160 mg daily; maximum: 640 mg/day ER (InnoPran XL®): initial, 80 mg once daily at bedtime (around 10 pm); maintenance:	Safety and efficacy in children have not been established.	Capsule (ER): 60 mg 80 mg 120 mg 160 mg Injection: 1 mg/ml Solution (IR): 20 mg/5 ml 40 mg/5 ml Tablet (IR): 10 mg 20 mg 40 mg 60 mg 80 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	may titrate dose up to 120 mg daily; maximum: 120 mg/day IR: initial, 40 mg twice daily; maintenance: gradually increase the dose up to 640 mg daily divided into 2-3 doses; usual dose is 120 to 240 mg/day divided into two to three doses; maximum: 640 mg/day Hypertrophic Subaortic Stenosis: ER (Inderal LA®): maintenance, 80 to 160 mg once daily IR: 20 to 40 mg three to four times daily before meals and at bedtime Migraine Prophylaxis: ER (Inderal LA®): initial, 80 mg once daily; maintenance: may increase dose gradually up to 160 to 240 mg once daily; usual dose is 160 to 240 mg once daily; maximum: 240 mg/day IR: initial, 80 mg daily in divided doses; maintenance: increase dose gradually up to 160 to 240 mg/day; maximum: 240 mg/day Pheochromocytoma: IR (operable tumors): 60 mg/day in divided doses for 3 days preoperatively as adjunct to alpha-adrenergic blockade Inoperable tumors: 30 mg/day in divided doses as adjunct to alpha-adrenergic blockade Post-Myocardial Infarction: IR: initial, 40 mg three times daily; maintenance: after 1 month, titrate up to 60 to 80 mg three times daily as tolerated; usual dose is 180 to 240 mg in divided doses; maximum: 240 mg/day		
Propranolol and hydrochlorothiazide	Hypertension: Initial: 40/25 mg twice daily;	Safety and efficacy in children have not been	Tablet: 40 mg-25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maintenance: may gradually increase dose until desired response is achieved up to 160 to 480 mg/day; maximum: 160 mg of propranolol	established.	80 mg-25 mg
Sotalol	Maintenance of Normal Sinus Rhythm: Betapace AF®: initial, 80 mg twice daily; maintenance: increase dose gradually with 3 days between increments up to 120 to a maximum of 160 mg twice daily Ventricular Arrhythmias: Betapace®: initial, 80 mg twice daily; maintenance: increase dose gradually with 3 days between increments up to 120 to 160 mg twice daily; maximum: 480 to 640 mg/day	Children >2 years of age: Maintenance of Normal Sinus Rhythm: Betapace AF®: initial, 30 mg/m^2 three times daily; maintenance: increase dose gradually with 3 days between increments up to 60 mg/m^2 three times daily; maximum: 60 mg/m^2 three times daily Ventricular Arrhythmias: Betapace®: initial, 30 mg/m^2 three times daily; maintenance: increase dose gradually with 3 days between increments up to 60 mg/m^2 three times daily; maximum: 60 mg/m^2 three times daily	Injection: 150 mg/10 ml Tablet: 80 mg 120 mg 160 mg 240 mg
Timolol	Hypertension: Initial: 10 mg twice daily; maintenance: increase dose gradually in 7 day increments up to 60 mg/day; usual dose is 20 to 40 mg/day; maximum: 60 mg/day divided into 2 doses Migraine Prophylaxis: Initial: 10 mg twice daily; maintenance: may increase dose up to 30 mg/day; maximum: 30 mg/day divided into 2 doses Post-Myocardial Infarction: 10 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg

ER=extended-release, IR=immediate release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the beta-adrenergic blocking agents are summarized in Table 17.

Table 17. Comparative Clinical Trials with the Beta-Adrenergic Blocking Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Angina				
Pandhi et al.[122] (1985) Acebutolol 100 to 400 mg TID vs propranolol 40 to 160 mg TID vs placebo	DB, XO Patients with classical anginal symptoms of effort with at least 7 attacks per week and angina being stable for at least 8-12 weeks	N=24 18 weeks	Primary: Incidence of anginal attack, number of nitroglycerin tablets used, exercise tolerance and side effects	Primary: Both acebutolol and propranolol significantly reduced the incidence of anginal attacks per week compared to placebo (P<0.001 for both groups), but the difference between the 2 groups was not significant (P>0.05). Both acebutolol and propranolol significantly reduced the number of nitroglycerin tablets used per week compared to placebo (P<0.001 for both groups), but the difference between the 2 groups was not significant (P>0.05). Both acebutolol and propranolol significantly improved exercise tolerance compared to placebo (P<0.001), but the difference between the 2 groups was not significant (P>0.05). Side effects reported (i.e., insomnia, sweating, bitter taste, heart burn, and muscle weakness) were similar between the two treatment groups. Clinical significance of the side effects was not reported.
Kardas et al.[121] (2007) Betaxolol 20 mg QD vs metoprolol 50 mg BID	OL, PG, RCT Patients 40-75 years with ischemic heart disease NYHA class I-II, no prior β-blocker treatment and whose mental state enabled conscious participation in the study	N=112 8 weeks	Primary: Overall compliance Secondary: Drug effectiveness and health-related QOL	Primary: The overall compliance significantly higher in the betaxolol group compared to the metoprolol group (86.5±21.3% vs 76.1±26.3%, respectively; P=0.002). Secondary: There was not a significant difference in chest pain episodes observed between the betaxolol and metoprolol groups compared from baseline (0.42/week and 0.46/week change in episodes, respectively; P>0.05). Overall, QOL dimensions were similar among both treatment groups, with the exception of physical function in which a significantly greater improvement was observed in the betaxolol group compared to the metoprolol group (42.9 vs 15.2 patients improved, respectively; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
van der Does et al.[120] (1999) Carvedilol 25 to 50 mg BID vs metoprolol 50 to 100 mg BID	DB, MC, RCT Patients ≤80 years of age with CHD and chronic stable angina for ≥2 months, exertional angina with symptoms improving after taking short acting nitrates or after a period of rest, and 1 exercise test performed that was limited by moderate anginal pain	N=368 3 months	Primary: Moderate anginal pain and time to ST- 1-mm segment depression	Primary: Compared to baseline, both carvedilol and metoprolol significantly decreased time to anginal pain during exercise test (+77s [+20 to +140] and +76 [+25 to +155], respectively; P<0.001 for both). Compared to baseline, both carvedilol and metoprolol significantly decreased time to ST- 1-mm segment depression during exercise test (+75.5 s [+47 to +154 s] and +60 [0 to +146 s], respectively; P<0.001 for both). Carvedilol significantly improved the time to 1-mm ST-segment depression compared to metoprolol (RR, 1.386; 95% CI, 1.045 to 1.839; P<0.05)
Weiss et al.[118] (1998) Carvedilol 12.5 to 50 mg BID vs placebo	DB, MC, XO Patients with 2 stress tests which evoked ischemic signs and symptoms	N=122 12 weeks	Primary: Efficacy and safety	Primary: The carvedilol 25 mg and 50 mg groups significantly reduced the time to angina compared to placebo (25 mg: 337 s, P=0.0039; 50 mg: 345 s; P<0.001 vs 316 s). The carvedilol 25 mg and 50 mg groups significantly reduced the time to 1-mm ST-segment depression compared to placebo (25 mg: 313 s; 50 mg: 323 s vs 301 s [P<0.0001 for both]). The percentage of patients reporting any adverse experience was slightly less in those receiving placebo (placebo: 28.4%; 12.5 mg: 33.1%; 25 mg: 34.5%; 50 mg: 31.9%). Adverse events included dizziness, fatigue, headache, dyspepsia and any hypotensive event. The clinical significance of the adverse events was not reported.
Hauf-Zachariou et al.[119] (1997) Carvedilol 25 mg BID	DB, MC, PG, RCT Patients 18-75 years with a confirmed diagnosis of coronary artery	N=313 12 weeks	Primary: Total exercise time, time to onset of angina, and time to 1 mm ST-segment	Primary: There was not a significant difference in total exercise time observed between the carvedilol (increased from 378 s to 436 s) and verapamil (increased from 386 s to 438 s) groups (RR, 1.14; 90% CI, 0.85±1.52). There was not a significant difference observed between the carvedilol and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs verapamil 120 mg TID	disease, exertional chest pain relieved by rest or glyceryl trinitrate for ≥2 months and 2 exercise tests with signs and symptoms of ischemia		depression, blood pressure, heart rate and rate pressure product	verapamil groups in time to onset of angina (increase from 296 s to 325 s vs 285 s to 326 s) and in time to 1 mm ST-segment depression (increase from 267 s to 298 s vs 286 s to 302 s). At peak exercise and at maximum comparable workload, carvedilol significantly reduced SBP (from 175 to 166 mm Hg) compared to verapamil (from 173 to 173 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced heart rate (from 123 to 112 mm Hg) compared to verapamil (from 124 to 120 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced rate pressure product (from 21564 to 18802 mm Hg) compared to verapamil (from 21488 to 20992 mm Hg)).
Savanitto et al.[123] (1996) <u>Weeks 1-6</u>: Metoprolol ER 200 mg QD vs nifedipine 20 mg BID <u>Weeks 7-10</u>: Metoprolol ER 200 mg QD plus placebo vs metoprolol ER 200 mg QD and nifedipine 20 mg	DB, MC, RCT Patients with typical angina1 symptoms that had been stable for ~6 months, who showed a positive response to exercise stress testing with 23 min of exercise tolerance and were in sinus rhythm and had an analyzable ST segment on electrocardiography	N=280 6 weeks	Primary: Angina frequency, exercise tolerance, and safety	Primary: At week 6, both metoprolol (mean change, –1.95; 95 % CI, –1.25 to –2.64) and nifedipine (mean change, –1.57; 95 % CI, –0.69 to –2.45) significantly reduced the frequency of angina compared to baseline, but there was not a statistical difference between groups. At the end of 10 weeks, there was not a statistical difference observed between the groups. At week 6, both metoprolol and nifedipine significantly increased the mean exercise time to l-mm ST-segment depression compared to baseline (both P<0.01); but metoprolol was significantly more effective than nifedipine (P<0.05). At week 10, the groups randomized to combination therapy had a further increase in time to l-mm ST-segment depression (P<0.05 vs placebo). There were 14 cardiovascular events including 1 sudden death, 3 acute myocardial infarctions, 8 cases of unstable angina, 1 of syncope and 1 of stroke and the incidence of these events did not differ among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID vs nifedipine 20 mg BID plus placebo				
Arrhythmias				
Lee et al.[116] (2008) Amiodarone vs sotalol vs β-blockers (agents not specified) Doses of the agents were not specified	RETRO Patients with atrial fibrillation and/or CHF (NYHA class ≥III) and an implantable cardioverter defibrillator	N=55 2.6 years	Primary: Cumulative rates of inappropriate shocks	Primary: Amiodarone demonstrated a significantly lower rate of inappropriate shock was compared β-blocker group (27.3% vs 70.6% at 4 years; P=0.003). This demonstrated an 83% reduction compared to the β-blockers (HR, 0.17; 95% CI, 0.05 to 0.64; P=0.008). There was not a significant difference in rates of inappropriate shocks observed between the amiodarone and sotalol groups (27.3% vs 54.3% at 4 years; P=0.29). There was not a significant difference in rates of inappropriate shocks observed between the sotalol and β-blocker groups (54.3% vs 70.6% at 4 years; P=0.16).
Connolly et al.[117] (2006) OPTIC β-blocker (bisoprolol, carvedilol or metoprolol) vs sotalol 240 mg/day	DB, MC, RCT Patients who received an implantable cardioverter defibrillator within 21 days of randomization, had sustained ventricular tachycardia, ventricular	N=412 12 months	Primary: implantable cardioverter defibrillator shock for any reason	Primary: Shocks occurred in 41 patients (38.5%) in the β-blocker group, 26 (24.3%) in the sotalol group, and 12 (10.3%) in the amiodarone plus β-blocker group. A reduction in the risk of shock was observed with use of amiodarone plus β-blocker or sotalol vs β-blocker alone (HR, 0.44; 95% CI, 0.28 to 0.68; P<0.001). The amiodarone plus β-blocker group significantly reduced the risk of shock compared with β-blocker alone (HR, 0.27; 95% CI, 0.14 to 0.52; P<0.001) and sotalol (HR, 0.43; 95% CI, 0.22 to 0.85; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in two to three divided doses vs amiodarone 200 mg QD plus β-blocker (bisoprolol, carvedilol or metoprolol) Amiodarone was loaded at 400 mg BID for 2 weeks, followed by 400 mg/day for 4 weeks, and then 200 mg/day until then end of the study	fibrillation or cardiac arrest, LVEF ≤40%, inducible ventricular tachycardia or ventricular fibrillation by programmed ventricular stimulation with LVEF ≤40% or unexplained syncope with ventricular tachycardia or ventricular fibrillation, inducible by programmed stimulation			Sotalol did not significantly reduce the risk of shock compared to the β-blocker alone group (HR, 0.61; 95% CI, 0.37 to 1.01; P=0.055).
Balcetyte-Harris et al.[115] (2002) Esmolol 0.5 mg/kg over 5 minutes then 0.05 mg/kg/min titrated to heart rate of 55 to 65 bpm and SBP >100 mm Hg for up to 24 hours vs oral β-blocker	OL, RCT Patients referred for elective CABG without concomitant valve replacement who were in sinus rhythm	N=50 72 hours	Primary: Development of atrial fibrillation lasting >30 mins Secondary: Development of adverse events, hypotension (SBP <90 mm Hg), symptomatic bradycardia or CHF (LV failure)	Primary: There was not a significant difference in development of atrial fibrillation after CABG between the esmolol and β-blocker group (7 [26%] patients' vs 6 [26%] patients, respectively). Secondary: Significantly more patients in the esmolol group experienced significant adverse events compared to the patients in the β-blocker group (11 [41%] vs 1 [4%] patients, respectively; P=0.006). Significantly more patients in the esmolol group experienced hypotension compared to the patients in the β-blocker group (8 vs 1 patient, respectively; P=0.03). There was not a statistically significant difference between the esmolol and the β-blocker group in the development bradycardia requiring pacing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(metoprolol ≥50 mg/day was the preferred agent)				(2 vs 0 patients, respectively) and in LV failure (1 vs 0 patients, respectively).
Kettering et al.[112] (2002) Metoprolol 25 to 200 mg/day vs sotalol 40 to 480 mg/day	PRO, RCT Symptomatic patients between 18 and 80 years with sustained ventricular tachycardia and/or ventricular fibrillation requiring an implantable cardioverter defibrillator	N=100 2 years	Primary: Ventricular tachycardia or ventricular fibrillation recurrence requiring implantable cardioverter defibrillator intervention Secondary: Total mortality	Primary: There was not a significant difference in ventricular tachycardia/ ventricular fibrillation recurrence rates observed between the metoprolol group (33 patients) and the sotalol group (30 patients; P=0.68). After 1 year of treatment, 46.3% of patients in the metoprolol group and 54.7% of patients in the sotalol group were free of a recurrence of ventricular tachycardia or ventricular fibrillation (P=0.68). After 2 years, rates were 31.5% and 36.6%, respectively. Secondary: There was not a significant difference in mortality rates observed between the metoprolol group (8 deaths) and the sotalol group (6 patients; P=0.43).
Seidl et al.[113] (1998) Metoprolol 50 mg/day vs sotalol 80 mg/day The doses of the study medications were titrated to the maximum titrates dose.	OL, RCT Patients >18 years of age requiring treatment if life-threatening ventricular tachycardia/ ventricular fibrillation who required an implantable cardioverter defibrillator due to non-inducible or drug refractory (≥1 unsuccessful antiarrhythmic trial) arrhythmias	N=70 26±16 months	Primary: Recurrence of ventricular tachycardia requiring antitachycardia pacing, fast ventricular tachycardia or ventricular fibrillation requiring implantable cardioverter defibrillator, discharges, and total mortality	Primary: Actuarial rates for absence of ventricular tachycardia recurrence were significantly higher in the metoprolol group vs the sotalol group at 1 and 2 years (83% and 80% vs 57% and 51%, respectively; P=0.016). Actuarial rates for absence of recurrence of a fast ventricular tachycardia or ventricular fibrillation were significantly higher in the metoprolol group vs the sotalol group 1 and 2 years (88% and 80% vs 54% and 46%, respectively; P=0.002) Actuarial survival rates at 1 and 2 years were not significantly different between the metoprolol and sotalol groups (94% and 91% vs 86% and 83%, respectively; P=0.287)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Steeds et al.[114] (1999) Sotalol 80 mg BID vs atenolol 50 mg QD	OL, PRO, RCT, XO Symptomatic patients over 50 years of age with paroxysmal atrial fibrillation documented on electrocardiogram	N=47 2 months	Primary: Frequency of paroxysmal atrial fibrillation Secondary: Average and total duration of paroxysmal atrial fibrillation, total ectopic count and symptom assessments	Primary: There was not a significant difference in frequency of episodes of paroxysmal atrial fibrillation observed between the sotalol and atenolol groups (median difference 0 min, 95% CI, 0 to 1; P=0.47). Secondary: There was not a significant difference in average duration of episodes of paroxysmal atrial fibrillation observed between the sotalol and atenolol groups (median difference, 0 min; 95% CI, 0 to 1 min; P=0.31) or in total duration of episodes of paroxysmal atrial fibrillation (median difference, 0 min; 95% CI, −1 to 2 min; P=0.51). There was not a significant difference in total ectopic count observed between the sotalol and atenolol groups (median difference, –123; 95% CI, −362 to 135; P=0.14) during either treatment period. There was not a significant difference in tolerance and symptom scores observed between the sotalol and atenolol groups (median difference, –5; 95% CI, −20 to 5; P=0.26)
Essential Tremor				
Calzetti et al.[131] (1981) Metoprolol 150 mg/dose vs propranolol 120 mg/dose vs placebo	DB, PC, RCT Patients 19-72 years with essential tremor and symptomatic for ≥1 year prior to the study	N=23 3 weeks	Primary: Tremor magnitude, heart rate and blood pressure	Primary: Both metoprolol (47±9.7%) and propranolol (55±5.0%) significantly decreased tremor magnitude from baseline compared to placebo (22±7.3%; P<0.01 for both treatments compared to placebo), but there was not a significant difference observed between the metoprolol and propranolol groups. Both propranolol (0.073) and metoprolol (0.01) significantly diminished the normal increase in pulse rate on standing (P<0.01) and placebo had no effect on such pulse rate. There was not a significant difference observed between the metoprolol and propranolol groups. Both metoprolol and propranolol significantly reduced the SBP from baseline compared to placebo, in the supine and standing positions (P<0.05).
Yetimalar et al.[132] (2005)	DB, RCT, XO	N=38	Primary: Tremor and global	Primary: After 30 days, both propranolol and olanzapine significantly reduced the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Propranolol 120 mg/day vs olanzapine 20 mg/day	Patients with essential tremor and previous therapy with ≥1 medications for essential tremor without significant benefit, which was withdrawn ≥1 month before study drug was given	74 days	QOL	all tremor evaluation measures (i.e., speaking, eating, dressing, writing working, etc) compared to baseline (P=0.000), but at the end of the study, olanzapine significantly improved all tremor evaluation measures (P<0.05) except hygiene (P =0.08) as compared to propranolol. Both propranolol (63%) and olanzapine (87%) significantly improved global QOL from baseline, but olanzapine significantly improved the global QOL score compared to propranolol (4.5±0.7 vs 3.6±0.9; P=0.000).
Gironell et al.[133] (1999) Propranolol 40 mg TID vs gabapentin 400 mg TID vs placebo	DB, PC, XO Patients with moderate to severe essential tremor that was chronic (≥5 years), persistent, and bilateral postural tremor with or without kinetic tremor involving hands or forearms, with no other neurological abnormalities or explanation for tremor	N=16 66 days	Primary: Tremor Clinical Rating Scale, accelerometric recordings, self-reported disability scale	Primary: Both gabapentin and propranolol significantly reduced the clinical examination and motor task performance components of the Tremor Clinical Rating Scale compared to placebo (−3.10±1.10; P=0.01 and −4.50±1.10; P=0.001, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.40±1.16; P=0.23). Both gabapentin and propranolol significantly reduced the activities of daily living component of the Tremor Clinical Rating Scale compared to placebo (−3.03±1.46; P<0.05 and −4.95±1.46; P=0.002, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.92±1.46; P=0.20). Both gabapentin and propranolol significantly reduced the patient's subjective assessment of the Tremor Clinical Rating Scale compared to placebo (1.37±0.46; P=0.006 and 1.44±0.46; P=0.004, respectively). Significant differences were not observed between the gabapentin and the propranolol groups (−0.07±0.46; P=0.89). Both gabapentin and propranolol significantly reduced the absolute power of the dominant frequency peak of accelerometry compared to placebo (–2352.0±1153.3; P=0.05 and -2282.14±1116.58; P=0.05, respectively), but significant differences were not observed between the gabapentin and the propranolol groups (−70.39±1165.22; P=0.95. Gabapentin significantly reduced the self-reported disability scale score

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more than placebo (−6.04±2.75; P=0.04) and propranolol did not (−4.48±2.75; P=0.11), but there were no significant differences between the gabapentin and propranolol groups (−1.55±2.75; P=0.58).
Heart Failure				
CIBIS Investigators and Committees[93] (1994) CIBIS Bisoprolol 1.25 to 5 mg QD vs placebo All patient received standard therapy (diuretic and vasodilator)	DB, MC, PC, PG, RCT Patients 18-75 years with NYHA functional class III or IV due to idiopathic dilated cardiomyopathy, ischemia, hypertension or valvular heart disease, a LVEF of <40%, and background therapy with a diuretic and a vasodilator	N=641 1.9 years	Primary: Total mortality Secondary: Tolerability and analysis critical events	Primary: There was no statistical significance between bisoprolol and placebo in total mortality (53 vs 67; RR, 0.80; 95% CI, 0.56 to 1.15; P=0.22). Secondary: Bisoprolol was well tolerated with no between group difference in premature treatment withdrawals (82 on placebo, 75 on bisoprolol; not significant). Significantly fewer patients in the bisoprolol group required hospitalization for cardiac decompensation (90 in placebo versus 61 in bisoprolol; P<0.01), and more patients improved by at least one NYHA functional class (48 on placebo versus 68 on bisoprolol; P=0.04) by the end of follow-up period.
CIBIS-II Investigators and Committees[94] (1999) CIBIS-II Bisoprolol 1.25 to 10 mg QD added to usual therapy (diuretic and vasodilator) vs	DB, MC, PC, RCT Symptomatic patients 18-80 years in NYHA class III or IV, with LVEF of 35% or less receiving standard therapy with diuretics and ACE inhibitor or other vasodilator	N=2,647 1.3 years	Primary: All-cause mortality Secondary: All-cause hospital admissions, cardiovascular mortality, cardiovascular mortality and cardiovascular hospital admissions (composite endpoint) and	Primary: CIBIS-II was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit. All-cause mortality was significantly lower with bisoprolol than on placebo (156 [11.8%] vs 228 [17.3%] deaths, respectively; HR, 0.66; 95% CI, 0.54 to 0.81; P<0.0001). Significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3.6%] vs 83 [6.3%] deaths, respectively; HR, 0.56; 95% CI, 0.39 to 0.80; P=0.0011). Secondary: All-cause hospital admissions was significantly lower with bisoprolol than on placebo (440 [33%] vs 513 [39%] patients, respectively; HR, 0.80; 95% CI, 0.71 to 0.91; P=0.0006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			permanent premature treatment withdrawals	All- cardiovascular deaths was significantly lower with bisoprolol than on placebo (119 [9%] vs 161 [12%] patients, respectively; HR, 0.71; 95% CI, 0.56 to 0.90; P=0.0049). Occurrence of composite endpoints of all cardiovascular deaths and cardiovascular admissions was significantly lower with bisoprolol than on placebo (388 [29%] vs 463 [35%] patients, respectively; HR, 0.79; 95% CI, 0.69 to 0.90; P=0.0004). Occurrence of treatment withdrawals was not statistically different between bisoprolol and the placebo group (194 [15%] vs 192 [15%] patients, respectively; HR, 1.00; 95% CI, 0.82 to 1.22; P=0.98).
Willenheimer et al.[103] (2005) CIBIS-III Bisoprolol 1.25 to 10 mg QD vs enalapril 2.5 to 10 mg BID	BE, MC, OL, PG, RCT Patients ≥65 years with stable mild to moderate CHF (NYHA II-III), LVEF of ≤35% at least 3 months prior to randomization, not on an ACE inhibitor, β-blocker or ARB therapy and no clinically relevant fluid retention of diuretic adjustment within the 7 days prior to randomization	N=1,010 1.22±0.42 years	Primary: Combined all-cause mortality or hospitalization Secondary: Combined end point at the end of the monotherapy phase and the individual components of the primary end point, cardiovascular death and cardiovascular hospitalization, permanent treatment cessation and the need for early introduction of the second drug as indicators of drug tolerability.	Primary: There were 178 patients (35.2%) with a primary end point of combined all-cause mortality or all-cause hospitalization in the bisoprolol-first group, compared to 186 (36.8%) patients in the enalapril-first group (absolute difference: –1.6%; 95% CI, –7.6 to 4.4%; HR, 0.94; 95% CI, 0.77 to 1.16; non-inferiority for bisoprolol-first vs enalapril-first treatment; P=0.019). Secondary: The combined endpoint at the end of the monotherapy phase occurred in 109 patients in the bisoprolol-first group compared to 108 patients in the enalapril-first group (HR, 1.02; 95% CI, 0.78 to 1.33; between-group difference P=0.90); 23 vs 32 patients died, respectively (HR, 0.72; 95% CI, 0.42 to 1.24; between-group difference P=0.24); and 99 vs 92 patients had been a hospitalization, respectively (HR, 1.08; 95% CI, 0.81 to 1.43; between-group difference P=0.59). There were 65 deaths in the bisoprolol-first group, as compared with 73 in the enalapril-first group (HR, 0.88; 95% CI, 0.63 to 1.22; between-group difference P=0.44). In the bisoprolol-first group, 151 patients were hospitalized, compared to 157 patients in the enalapril-first group (HR, 0.95; 95% CI, 0.76 to 1.19; between-group difference P=0.66).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was not a significant difference in cardiovascular death rate observed between the bisoprolol-first (55) and enalapril-first (56) treatment groups (HR, 0.97; 95% CI, 0.67 to 1.40; between-group difference P=0.86). During the monotherapy phase, 35 (6.9%) patients in the bisoprolol-first group permanently discontinued therapy, compared to 49 (9.7%) patients in the enalapril-first group. During the combined-therapy phase, 19 patients (4.2%) in the bisoprolol-first group permanently discontinued bisoprolol therapy and 47 (10.4%) discontinued enalapril therapy. In the enalapril-first group, 24 patients (5.5%) permanently discontinued bisoprolol and 16 (3.7%) discontinued enalapril. There was not a statistical significant difference observed in the early introduction of the second drug between the bisoprolol-first group (39 [7.7%] patients) compared to the enalapril-first group (37 [7.3%] patients; P=0.81).
Packer et al.[96] (2001) COPERNICUS Carvedilol 3.125 to 25 mg BID vs placebo	DB, MC, PC, RCT Patients with severe chronic heart failure as a result of ischemic or nonischemic cardiomyopathy, dyspnea or fatigue at rest or on minimal exertion for ≥2 months and a LVEF <25% despite appropriate conventional therapy with diuretics, and an ACE inhibitor, or ARB	N=2,280 10.4 months	Primary: Total mortality Secondary: Combined risk of death or hospitalization for any reason and withdrawal rates	Primary: The study was stopped early due to statistical significance. The annual mortality in the placebo group was 19.7% (190) versus 12.8% (130 deaths) in the carvedilol group, a 35% reduction in mortality (95% CI, 19 to 48%; P<0.00013). Secondary: Carvedilol reduced the combined risk of death or hospitalization for any reason by 24% compared to placebo (425 vs 507 patients; 95% CI, 13 to 33%; P<0.001) Withdrawal rates were significantly higher in the placebo group compared to the carvedilol group (18.5 vs 14.8; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dargie et al.[97] (2001) CAPRICORN Carvedilol 6.25 to 25 mg bid mg vs placebo	DB, MC, PC, RCT Patients 18 years and older with a stable myocardial infarction occurring 3 to 21 days prior to randomization, LVEF ≤40% and ACE inhibitor therapy for ≥48 hours	N=1,959 1.3 years	Primary: All-cause mortality, and all-cause mortality or cardiovascular hospital admissions Secondary: Sudden death, hospital admission for heart failure, recurrent nonfatal myocardial infarction, and all-cause mortality or recurrent nonfatal myocardial infarction.	Primary: There was not a significant difference observed between the carvedilol and placebo groups in the combined endpoint of all-cause mortality and hospital admissions due to cardiovascular events (340 [35%] vs 367 [37%], respectively; HR, 0.92; 95% CI, 0.80 to 1.07; P=0.296). All-cause mortality alone was statistically better in the carvedilol group than the placebo group (116 [12%] vs 151 [15%], respectively; HR, 0.77; 95% CI, 0.60 to 0.98; P=0.031). Secondary: There was not a significant difference observed between the carvedilol and placebo groups in sudden death (51 [5%] vs 69 [7%], respectively; HR, 0.74; 95% CI, 0.51 to 1.06; P=0.098) or in hospital admissions for heart failure (118 [12%] vs 138 [14%], respectively; HR, 0.86; 95% CI, 0.67 to 1.09; P=0.215). The carvedilol group, compared to placebo, experienced significantly lower rates of nonfatal myocardial infarctions (34 [3%] vs 57 [6%], respectively; HR, 0.59; 95% CI, 0.39 to 0.90; P=0.014) and all-cause mortality or recurrent nonfatal myocardial infarction (139 [14%] vs 192 [20%], respectively; HR, 0.71; 95% CI, 0.57 to 0.89; P=0.002).
Bristow et al.[98] (1996) Carvedilol 6.25 mg BID vs carvedilol 12.5 mg BID vs carvedilol 25 mg BID	DB, MC, PC, RCT Symptomatic (≥3 months) patients, 18-85 years with stable heart failure from ischemic or nonischemic dilated cardiomyopathy, an LVEF of ≤35%, a 6-minute walk test between 150 to 425 m and on stable doses of diuretics and ACE inhibitors	N=345 6 months	Primary: Submaximal exercise improvement Secondary: Minnesota questionnaire, changes in NYHA functional class, changes in LVEF, hospitalization, and changes in signs and symptoms of heart failure,	Primary: There were no differences on submaximal exercise with any dose compared to placebo. Walk distances between in each group ranged between 300 to 400 m in both the 6-minute and 9-minute walk tests; P=0.50 and P=0.27, respectively). Secondary: There were no significant changes in the overall Minnesota Questionnaire scores incorporating both physical and emotional dimensions (changes from baseline in the placebo and low-, medium-, and high-dose carvedilol groups of –7.3, –7.9, –7.3, and –6.6, respectively; P=0.512 in difference from placebo). There were no significant improvements in NYHA functional classes in the carvedilol groups compared to placebo (actual values not reported;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients remained on their standard medications.	for 2 weeks before baseline testing		occurrence of adverse clinical experiences and survival	P=0.64). Carvedilol treatment resulted in a dose-related significant improvement in LVEF; carvedilol 6.25 mg (~5 EF units; P<0.005), 12.5 mg (~6 EF units; P<0.005) and 25 mg (~7.5 EF units; P<0.0001) compared to placebo (2 EF unit improvement). The mean number of hospitalizations per patient were significantly reduced in each of the carvedilol groups (~0.1 hospitalizations) compared to placebo (~0.35; P<0.01). Bradycardia was significantly higher in the carvedilol 12.5 mg group (10 [11%]) and the 25 mg group (10 [11%]) compared to placebo (1 [1%]; P<0.05). Also, dizziness was significantly higher in the carvedilol 25 mg group (34 [38%]) compared to the placebo group (19 [23%]; P<0.05). The clinical significance of these advents was not mentioned. There was a dose-related, statistically significant reduction in mortality in the carvedilol-treated groups, with respective mortality rates of 6.0% for the carvedilol 6.25 mg group (RR, 0.356; 95% CI, 0.127 to 0.998; P<0.05), 6.7% for the 12.5 mg group (HR, 0.416; 95% CI, 0.158 to 1.097; P=0.07), and 1.1% in the 25 mg group (HR, 0.067; 95% CI, 0.009 to 0.512; P<0.001) compared to 15.5% mortality in the placebo group. Combining all three carvedilol arms of the study compared to the placebo arm showed statistical significance in all-cause mortality, risk reduced by 73% (P<0.001).
Poole-Wilson et al.[107] (2003) COMET Carvedilol 25 mg BID vs	DB, PG, MC, RCT Patients with NYHA II–IV heart failure, admission for a cardiovascular reason in the previous 2 years, an LVEF of <35%, and were stable and	N=3,029 58 months	Primary: All-cause mortality and the composite endpoint of mortality or all-cause admission	Primary: All-cause mortality was significantly lower in the carvedilol group compared to the metoprolol group (512 [34%] vs 600 [40%], respectively; HR, 0.83; 95% CI, 0.74 to 0.93; P=0.0017). Cardiovascular deaths were significantly lower in the carvedilol group compared to the metoprolol group (438 [29%] vs 534 [35%], respectively; HR, 0.80; 95% CI, 0.70 to 0.90; P=0.0004). There was not a significant difference in the composite endpoints of all-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metoprolol 50 mg BID	optimized with diuretics for ≥2 weeks and ACE inhibitor for ≥4 weeks unless not tolerated			cause mortality or all-cause admission observed between the carvedilol and metoprolol groups (1,116 [74%] vs 1,160 [76%], respectively; HR, 0.94; 95% CI, 0.86 to 1.02; P=0.122).
Packer et al.[108] (2001) Carvedilol 50 to 100 mg/day vs metoprolol 50 to 150 mg/day or metoprolol ER 150 to 200 mg/day or placebo	MA Nineteen trials evaluating patients with NYHA class of II or III and left ventricular EF dysfunction	N=2,779 8.3 months	Primary: Change in LVEF	Primary: In the 6 placebo-controlled trials, metoprolol significantly increased the mean LVEF by 0.063±0.002 compared to the increase with placebo of 0.025±0.001 (difference of 0.038±0.005; P<0.0001). In the 9 placebo-controlled trials, carvedilol significantly increased the mean LVEF by 0.079±0.001 compared to the increase with placebo of 0.012±0.001 (difference of 0.065±0.005; P<0.0001). Comparing the two agents, carvedilol increased the LVEF significantly greater than metoprolol (difference of 0.026±0.007; P=0.0002). In the 4 direct comparator trials, carvedilol significantly increased the mean LVEF by 0.089±0.002 compared to the increase with metoprolol of 0.055±0.002 (difference of 0.029±0.011; P=0.009).
Arumanayagam et al.[109] (2001) Carvedilol 25 mg BID vs metoprolol 50 mg BID	DB, RCT Symptomatic Chinese patients with CHF and LVEF of <45%	N=24 12 weeks	Primary: Plasma total antioxidant status, erythrocyte superoxide dismutase and glutathione peroxidase	Primary: Neither carvedilol nor metoprolol significantly reduced total antioxidant status activities after 12 weeks of therapy (1.65±0.06 to 1.68±0.09 mmol/L and 1.44±0.05 to 1.51±0.06 mmol/L, respectively). Carvedilol significantly reduced erythrocyte superoxide dismutase activity after 12 weeks of therapy, (986±46 to 871±22 U/g Hb; P <0.001), but metoprolol did not (790±43 to 836±46 U/g Hb). Carvedilol significantly reduced glutathione peroxidase activity after 12 weeks of therapy, (145±7 to 132±9 U/g Hb; P <0.05), but metoprolol did not (143±8 to 138±9 U/g Hb).
Sanderson et al.[110] (1999)	DB, PG, RCT Symptomatic	N=51 12 weeks	Primary: Symptom score (QOL	Primary: A significant improvement in symptom scores from baseline were experienced in both the carvedilol (17.2±3 to 8.1±2; P<0.001) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Carvedilol 25 mg BID vs metoprolol 50 mg BID All patients continued on their standard therapy.	patients with CHF, LVEF of <45%, and on standard therapy (diuretics, digoxin and ACE inhibitor)		questionnaire and NYHA class), exercise tolerance time, and LVEF	metoprolol (13.1±1.8 to 4.8±1.4; P<0.001) groups, but there was not a significant difference between the agents. A significant improvement in NYHA class from baseline were experienced in both the carvedilol (2.6±0.11 to 2.2±0.12; P<0.001) and metoprolol (2.7±0.09 to 2.1±0.09; P<0.001) groups, but there was not a significant difference between the agents. A significant improvement in exercise tolerance time from baseline were experienced in both the carvedilol (1122±51 to1194±63; P<0.05) and metoprolol (1164±46 to 1263±52; P<0.01) groups, but there was not a significant difference between the agents. A significant improvement in LVEF from baseline were experienced in both the carvedilol (26±1.8 to 35±2.6; P<0.001) and metoprolol (25±1.8 to 31±2.5; P<0.001) groups, but there was not a significant difference between the agents.
Lechat et al.[99] (1998) β-blockers (bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol) vs placebo	MA Patients with NYHA I-IV chronic heart failure	N=3,023 (18 trials) 1.5-15 months	Primary: All-cause mortality, hospitalizations due to heart failure, combination of all-cause mortality and hospitalizations for worsened heart failure, changes in functional status and changes in LVEF	Primary: All endpoints showed a significant effect for β-blockers (P<0.05). β-blockers demonstrated a 32% reduction in risk of death compared to placebo (130 vs 156 deaths; 95% CI, 12% to 47%; P=0.003). β-blockers demonstrated a 41% reduction in hospitalizations due to heart failure compared to placebo (166 vs 223 hospitalizations; 95% CI, 26% to 52%; P<0.001). β-blockers demonstrated a 37% reduction in the combination of mortality and morbidity compared to placebo (239 vs 293; 95% CI, 24% to 49%; P<0.001). β-blockers demonstrated a 32% increase in the likelihood of improvement in NYHA class (95% CI, 1% to 74%; P=0.04) and a 30% decrease in the likelihood of worsening NYHA (95% CI, 4% to 50%; P=0.03) compared to placebo β-blockers demonstrated a 29% increase in ejection fraction compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				placebo (0.23±0.04 vs 0.31±0.04; P<10–9). β-adrenergic agents did not differ in respect to any outcome measure except that reduction in mortality risk. Beta selective agents were less robust than the nonselective agents (P=0.049).
Brophy et al.[100] (2001) β-blockers (bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol) vs placebo	MA Patients with CHF of various etiologies	N=10,135 (22 trials) 3-23 months	Primary: Overall mortality and hospitalizations for CHF	Primary: β-blockers significantly reduced mortality compared to placebo (444 vs 624; OR, 0.65; 95% CI, 0.53 to 0.80). β-blockers significantly reduced hospitalizations due to CHF compared to placebo (540 vs 754; RR, 0.64; 95% CI, 0.53 to 0.79). The probability that β-blocker therapy reduced total mortality and hospitalizations for congestive heart failure was almost 100%. The best estimates of these advantages are 3.8 lives saved and 4 fewer hospitalizations per 100 patients treated in the first year after therapy. The probability that these benefits are clinically significant (>2 lives saved or >2 fewer hospitalizations per 100 patients treated) is 99%.
Whorlow et al.[101] (2000) β-blockers (bisoprolol, bucindolol, carvedilol metoprolol, nebivolol) vs placebo	MA Patients with NYHA class IV heart failure currently taking background therapy (ACE inhibitors and diuretics with or without digoxin)	N=8,119 (18 trials) 3-21 months	Primary: Mortality in NYHA class IV patients	Primary: β-blockers demonstrated a 29% reduction in mortality compared to placebo in patients with NYHA class IV (RR, 0.71; 95% CI, 0.52 to 0.96). The 29% risk reduction is similar to risk reduction seen with β-adrenergic blockers in other NYHA classes. β-blockers demonstrated a 32% reduction in mortality compared to placebo in patients with NYHA I-IV (HR, 0.68; 95% CI, 0.61 to 0.77).
Bouzamondo et al.[102] (2003) β-blockers (bisoprolol,	MA Randomized controlled evaluating patients with heart failure	N=not specified Duration varied	Primary: Overall mortality and hospitalized for worsening heart failure	Primary: β-blockers reduced overall mortality by 22% compared to placebo (95% CI, 16% to 28%). β-blockers reduced hospitalizations due to worsening heart failure by 24% compared to placebo (95% CI, 20% to 29%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bucindolol, carvedilol, and metoprolol) vs placebo	depending on NYHA class			Benefits were similar for bisoprolol, metoprolol, and carvedilol regardless of NYHA class.
Jabbour et al.[138] (2010) β-blockers (bisoprolol, carvedilol, metoprolol)	OL, XO Patients with NYHA class I-III heart failure with a subgroup of patients with coexisting COPD	N=51 16 weeks	Primary: Post-bronchodilator forced expiratory volume in 1second (FEV_1)	Primary: FEV_1 was significantly higher in patients receiving bisoprolol vs carvedilol, both in those with coexisting COPD (P<0.01) and without (P=0.02). There was a significant difference between all patients receiving carvedilol versus those receiving metoprolol (P=0.04), however, when compared for coexisting COPD, there was no difference in FEV_1. There was no significant difference for all patients, those with COPD, or those with CHF only when metoprolol and bisoprolol were compared.
MERIT-HF Study Group[95] (1999) MERIT-HF Metoprolol CR/XL 12.5 mg up to 200 mg QD vs placebo	DB, MC, PC, RCT Symptomatic patients 40-80 years in NYHA class II-IV, with LVEF of 40% or less stabilized on standard therapy (diuretic and vasodilator)	N=3,991 1 year	Primary: All-cause mortality and all-cause mortality in combination with all-cause admission to hospital (time to first event)	Primary: Study was stopped early on the recommendation of the independent safety committee. All-cause mortality was significantly lower in the metoprolol CR/XL group than in the placebo group (145 [7.2%] vs 217 [11.0 %] deaths, RR, 0.66; 95% CI, 0.53 to 0.81; P=0.00009). There were significantly fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs 132; RR, 0.59; 95% CI, 0.45 to 0.78; P=0.0002) and deaths from worsening heart failure (30 vs 58; RR, 0.51; 95% CI, 0.33 to 0.79; P=0.0023). Study drug was permanently stopped early in 13.9% of the patients in the metoprolol CR/XL group and in 15.3% of patients in the placebo group (RR, 0.90; 95% CI, 0.77 to 1.06).
Di Lenarda et al.[104] (1999) Metoprolol 142±44 mg QD	OL, PG, RCT Symptomatic (>12 months) patients with stable dilated	N=30 12 months	Primary: Improvement in LV function and remodeling	Primary: LVEF significantly improved in the carvedilol group (+7±3%) compared with the metoprolol group (–1±2%; P=0.045). LV end-systolic volume was significantly improved in the carvedilol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs carvedilol 12.5 mg to 50 mg BID	cardiomyopathy, LVEF of ≤40% and who poorly responded to chronic treatment with metoprolol plus conventional therapy (metoprolol plus ACE inhibitor, digitalis, diuretics), persistent moderate-to-severe left ventricular dysfunction and reduced exercise tolerance		Secondary: Effects on symptoms, QOL, exercise tolerance and ventricular arrhythmias	group (–7±5) compared to the metoprolol group (+6±4 mL/m^2; P=0.047). There was not a significant difference in LV end-diastolic volume observed between the carvedilol (–8±7) and the metoprolol group (+7±6 mL/m^2; P=0.053). Secondary: There was not a significant difference observed in the NYHA class, the Heart Failure Score, the Minnesota "Living With Heart Failure" Questionnaire and submaximal exercise tolerance did not significantly change between the carvedilol and metoprolol groups. Carvedilol, compared to metoprolol, demonstrated a positive effect on ventricular ectopic beats (-12±9 vs +62±50 n/h; P=0.05) and couplets (–0.5±0.4 vs +1.5±0.6 n/h; P=0.048), but not a significant effect on episodes of nonsustained ventricular tachycardia (–0.02±0.03 vs +0.03±0.01).
Maack et al.[105] (2001) Metoprolol 12.5 to 100 mg BID vs carvedilol 3.125 to 25 mg BID	OL, XO Patients with stable NYHA class I-III heart failure due to ischemic or idiopathic dilated cardiomyopathy and an LVEF of <35%	N=80 6 months	Primary: Change in LVEF and change in baseline hemodynamic properties (left ventricular end diastolic, end systolic volume, NYHA class, etc.)	Primary: After 6 months of treatment, LVEF improved in the carvedilol group (32±3% to 36±4%; P<0.05 vs baseline) and in the metoprolol group (27±4% to 30±5%; P<0.05 vs baseline). There was not a statistical difference between the agents. There were no differences between the groups in left ventricular end diastolic, end systolic volume, NYHA functional class or any other hemodynamic parameters at rest.
Metra et al.[106] (2000) Metoprolol 5 to 100 mg BID vs carvedilol 3.125 to 50 mg BID	DB, PRO, RCT Symptomatic (≥6 months) patients with CHF caused by ischemic or nonischemic cardiomyopathy, NYHA II-IV, LVEF ≤35% and a peak VO2 ≤25 mL/kg-	N=150 15 months	Primary: Change in LVEF Secondary: Hemodynamic variables at rest and peak exercise, maximal and submaximal exercise tolerance, QOL, NYHA	Primary: Both agents significantly increased LVEF from baseline (P<0.001 for both), but carvedilol increased LVEF significantly greater at the than metoprolol (+10.9±11% vs +7.2±7.7%; P=0.038). Secondary: At the end of the study, both agents carvedilol and metoprolol increased stroke volume and stroke work indexes and decreased mean pulmonary artery pressure, pulmonary wedge pressure, and heart rate from baseline (all P<0.05 from baseline). However, the increase in stroke volume and stroke work indexes during exercise and the decreases in mean pulmonary

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients continued on their usual treatment for heart failure.	1/min-1 and on constant background therapy (furosemide and ACE inhibitor or ARB) for 1 week prior to the study		functional class, and the frequency of death and urgent transplantation	artery pressure and pulmonary wedge pressure at both rest and exercise were greater with carvedilol than with metoprolol (all P<0.05). Carvedilol increased rest and exercise cardiac index from baseline (both P<0.05). Heart rate declined with both drugs at rest and exercise, but the decrease in exercise heart rate with carvedilol was greater than with metoprolol (P<0.05 for the difference between the groups). Both metoprolol and carvedilol significantly improved NYHA class, 6-minute walk distance, and QOL scores from baseline (all P<0.05), and there were no differences between the 2 treatments. Overall, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent urgent transplantation.
Hypertension				
Reim et al.[82] (1985) Acebutolol 400 mg QD vs propranolol 160 mg QD	DB, MC, XO Patients 18-70 years with essential hypertension and blood pressure of >150/90 mm Hg	N=18 14 weeks	Primary: blood pressure and heart rate during ergometer exercise test	Primary: There was not a significant difference observed between the acebutolol and propranolol groups in decreases in blood pressure (systolic and diastolic) and heart rate at rest (P=0.123, P=0.230 and P=0.210, respectively). At the ergometer 25 watt load, heart rate and DBP were not significantly different between acebutolol and propranolol (P=0.087 and P=0.068, respectively), but SBP was significantly lower in the acebutolol group (P=0.042) At the higher ergometer loads of 50 and 75 watts, acebutolol had a significantly lower increase in SBP and heart rate compared to propranolol during exercise (50 watts: P=0.004 and P=0.012, respectively; 75 watts: P=0.005 and P=0.001, respectively), but there was not a significant difference observed between the groups in DBP in the 50 and 75 watt loads (P=0.057 and P=0.058, respectively). At the highest ergometer load of 100 watts, acebutolol significantly reduced systolic and DBPs and heart rate compared to propranolol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.003, P=0.001, and P=0.001, respectively).
Fogari et al.[35] (1984) Weeks 1-4: Atenolol 50 mg QD vs chlorthalidone 12.5 mg QD Weeks 5-study end: Atenolol 50 mg-chlorthalidone 12.5 mg QD	RCT, SB Patients 61-80 years inadequately controlled (SBP >170 mm Hg and/or DBP >100 mm Hg) on antihypertensive medications	N=38 6 months	Primary: Changes in blood pressure	Primary: After the first 4 weeks, atenolol (from 177.5 to 161.1 mm Hg) significantly reduced blood pressure compared to baseline, but chlorthalidone did not (from 176.6 to 179.1 mm Hg). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to previous therapies (P<0.001 for all comparisons). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to atenolol and chlorthalidone monotherapy (P<0.001 or P<0.01 for all comparisons). Mean blood pressure reduction obtained by the atenolol and chlorthalidone combination product was 30/15 mm Hg in the standing position (P<0.001). Serum potassium increased with atenolol-chlorthalidone (4.45 mEq/L) compared to chlorthalidone alone (4.01 mEq/L; P<0.001).
Leonetti et al.[36] (1986) Atenolol 50 mg QD vs atenolol 100 mg QD vs chlorthalidone 12.5 mg QD	DB, RCT Patients 24-68 years with mild to moderate hypertension (WHO stage I or II), with supine DBP ≥95 mm Hg at the end of the 4-week washout period	N=28 16 weeks	Primary: Changes in blood pressure	Primary: Mean supine blood pressure was significantly reduced in all treatment groups compared to placebo: 153±18/93±9 mm Hg for atenolol 50 mg patients, 155±22/91±8 mm Hg for atenolol 100 mg patients, 148±17/93±11 mm Hg for chlorthalidone 12.5 mg patients, and 144±16/89±6 mm Hg for the atenolol-chlorthalidone combination patients. All of the changes in blood pressure were significant (P<0.01) versus placebo. Supine SBP was lower with atenolol-chlorthalidone than with the atenolol 100 mg alone (P<0.05). Upright SBP was lower with atenolol-chlorthalidone than with atenolol 50 mg alone (P<0.05) and atenolol 100 mg alone (P<0.05). Mean supine heart rate was 77±7 bpm after placebo which decreased to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atenolol 50 mg-chlorthalidone 12.5 mg QD				69±10 bpm (P<0.01) after atenolol 50 mg, to 67±6 bpm (P<0.01) after atenolol 100 mg, to 77±10 bpm (P=not significant, was not reported) after chlorthalidone alone. Chlorthalidone alone demonstrated a significant reduction in serum potassium levels compared to placebo (3.88 vs 4.09 mEq/L; P<0.05) and no change when the atenolol-chlorthalidone combination was compared to placebo (3.98 vs 4.09; P=not significant, value was not reported). Chlorthalidone alone and atenolol-chlorthalidone demonstrated a significant increase in serum uric acid levels compared to placebo (4.90±1.52 mg/dL, 5.07±1.33 mg/dL, respectively, vs 4.24±1.12 for placebo; P<0.05 for both). All treatments were well tolerated. Some adverse events reported included dyspnea, precordial discomfort and cold extremities. Incidence, severity and P values were not reported.
Dhakam et al.[74] (2008) Atenolol 50 mg QD vs nebivolol 5 mg QD vs placebo QD	DB, RCT, XO Never-treated subjects with isolated systolic hypertension	N=16 17 weeks	Primary: Change in central blood pressure Secondary: Change in peripheral blood pressure, AIx, aPWV and N-terminal proBNP.	Primary: There was not a statistically significant difference observed in the change in aortic SBP between the nebivolol and atenolol groups (125±3 vs 127±3 mm Hg; P=0.4), but both agents were significantly better than placebo (131±2 mm Hg). There was not a statistically significant difference observed in the change in aortic DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; P=0.3), but both agents were better than placebo (82±2 mm Hg). Secondary: There was not a statistically significant difference observed in the change in brachial SBP between the nebivolol and atenolol groups (136±3 vs 137±3 mm Hg; P=0.4), but both agents were significantly better than placebo (149±3 mm Hg). There was not a statistically significant difference observed in the change in brachial DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; P=0.5), but both agents were better than placebo (82±2 mm Hg).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a statistically significant reduction in AIx in the atenolol group compared to the nebivolol group (32±2 vs 28±2%; P=0.4), but both agents were significantly better than placebo (22±2%). There was not a statistically significant difference observed in the reduction of aPWV in the atenolol group compared to the nebivolol group (8.9±0.3 vs 9.1±0.3 m/s; P=0.2), but both agents were significantly better than placebo (10.0±0.4 m/s; P was not reported). There was not a statistically significant difference observed in the rise in N-terminal pro-BNP in the atenolol group compared to the nebivolol group (157 vs 138 pg/mL; P=0.6), but both agents were significantly better than placebo (75 mg/mL).
Fogari et al.[75] (1997) Atenolol 50 mg QD vs nebivolol 5 mg QD	DB, PG, RCT Patients 18-70 years of age with stable type 2 diabetes (A1C ≤8% during previous 6 months with diet and/or oral therapy stable for ≥6 months), and mild to moderate hypertension (DBP ≥95 and <116 mm Hg) at the end of the 4-week run-in period with placebo	N=30 6 months	Primary: Changes in blood pressure, heart rate, 24-hour urinary C-peptide excretion, HbA_{1c}, plasma glucose, and lipid levels Secondary: Euglycemic hyperinsulinemic clamp test (body glucose utilization)	Primary: Both atenolol and nebivolol significantly reduced blood pressure and heart rate from baseline (P<0.001 for all measures), but there was not a significant difference between the treatment groups at weeks 0, 2 and 24 (P>0.05 for all measures). There no significant changes from baseline in mean 24-hour urinary C-peptide excretion, HbA_{1c}, plasma glucose, and lipid levels (P>0.05). There were also no significant differences observed between treatment groups in any of these measures (P>0.05). Secondary: There was not a significant decrease from baseline in mean values for whole body glucose utilization observed in neither the atenolol group nor the nebivolol group (mean decrease of 0.9% vs 2.6%, respectively; P>0.05) and the groups were significant from each other (P>0.05).
Dahlöf et al.[73] (1991) STOP-Hypertension Atenolol 50 mg QD, HCTZ 25 mg	DB, MC, RCT Swedish men and women 70-84 years old with treated or untreated essential hypertension defined as SBP	N=1,627 25 months	Primary: Frequency of stroke, myocardial infarction and other cardiovascular death	Primary: The active treatments significantly reduced the number of all primary endpoints (94 vs 58; RR, 0.60; 95% CI, 0.43 to 0.85; P=0.0031), frequency of stroke (53 vs 29; RR, 0.53; 95% CI, 0.33 to 0.86; P=0.0081) and frequency of other cardiovascular deaths (13 vs 4; RR, 0.30; 95% CI, 0.07 to 0.97) compared to placebo. There was not a statistically significant decrease observed in the rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs placebo	≥180 mm Hg with a DBP of ≥90 mm Hg, or DBP >105 mm Hg irrespective of the SBP measured on 3 separate occasions during a 1-month placebo run-in phase in previously untreated patients			myocardial infarction between the active treatments and placebo (28 vs 25; RR, 0.87; 95% CI, 0.49 to 1.56).
Nissinen et al.[38] (1980) Atenolol 100 mg QD plus chlorthalidone 25 mg QAM (single entity products) vs atenolol 100 mg-chlorthalidone 25 mg QAM (fixed-dose combination) vs placebo	DB, RCT Patients with newly diagnosed mild to moderate hypertension (supine DBP 100 mm Hg on ≥3 occasions)	N=23 16 weeks	Primary: Changes in blood pressure and heart rate	Primary: Each of the active drug combinations lowered standing, supine, and post-exercise blood pressure significantly compared to placebo at 2 and 4 weeks (P<0.001, P<0.01 and P<0.05). There was not a statistical difference between the active treatment regimens (P=NS). Each of the active drug combinations lowered standing, supine, and post-exercise heart rate significantly compared to placebo at 2 and 4 weeks (P<0.001, P<0.01 and P<0.05). There was not a statistical difference between the active treatment regimens (P=NS). Side effects did not differ between treatment groups and placebo in terms of frequency or severity. Reported side effects included dizziness, headache and tiredness.
Davidov et al.[81] (1988) Betaxolol 10 to 40 mg QD vs	DB, MC, RCT Patients 21-73 years with mild to moderate hypertension (supine DBP of 95-	N=141 24 weeks	Primary: Change in blood pressure and heart rate	Primary: Both betaxolol and propranolol significantly reduced SBP from baseline (7±2.5 and 7±2.0 mm Hg; P<0.01 for both). Both betaxolol and propranolol significantly reduced DBP from baseline (11±0.9 and 9±1.2 mm Hg; P<0.01 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
propranolol 40 to 160 mg BID	115 mm Hg)			Both betaxolol and propranolol significantly heart rate from baseline (6±1.3 and 7±1.1 bpm; P<0.01 for both). At the end of the study, there was not a significant difference in response between groups.
Czuriga et al.[77] (2003) NEBIS Bisoprolol 5 mg QD vs nebivolol 5 mg QD	MC, PG, RCT, SB Patients 30-65 years with mild to moderate hypertension, a DBP 95-110 mm Hg and a SBP ≤180 mm Hg at the end of the placebo run-in period who were either newly diagnosed or previously treated hypertensives and required a change of therapy in consequence of side-effects or poor compliance	N=273 16 weeks	Primary: Percentage of responders achieving DBP normalization (≤90 mm Hg) or a DBP reduction of at least 10 mm Hg and heart sitting rate Secondary: Adverse events and symptom questionnaire	Primary: There was not a significant difference between percentage of responders between the nebivolol group (92%) and the bisoprolol group (89.6%). There was not a significant difference in the mean change in blood pressure observed between the nebivolol and bisoprolol (SBP: −20.5±12.9 vs −20.0±12.0 mm Hg, respectively; P=0.7434) and DBP (−15.7±6.4 vs −16.0 ± 6.8 mm Hg, respectively; P=0.8230). There was not a significant difference in mean heart rate observed between the nebivolol (68.7 ± 8.5 per minute) and the bisoprolol group (68.1 ± 7.5 per minute). Secondary: There was not significant difference in rates of adverse events reported between the nebivolol (8 patients [5.8%]) and the bisoprolol group (12 patients [8.9%]; P>0.05). All adverse events were either mild (55%) or moderate (45%) in intensity. Both treatments demonstrated a significant reduction in the basal score index at visit 5 (nebivolol −0.7 vs bisoprolol −0.5; P<0.02), but there was no significant difference between treatment groups (P>0.05).
Stoschitzky et al.[84] (2006) Bisoprolol 10 mg on day 1, then 5 mg QD vs carvedilol 50 mg	DB, PC, RCT, XO Male patients between 22 and 34 years with a height between 177 and 189 cm, and body weight between 66 and 86 kg	N=16 1 week	Primary: Heart rate and blood pressure at rest and exercise Secondary: Effects on nocturnal melatonin release and QOL	Primary: Compared to baseline, heart rate at exercise was decreased at 3 hours after the first dose by bisoprolol (–24%), carvedilol (–17%) and nebivolol (–15%); (P<0.05 for each group). Bisoprolol was significantly better than nebivolol (P<0.05). Compared to baseline, heart rate at exercise was decreased at 24 hours after the first dose by bisoprolol (–18%), carvedilol (12 hours; –15%) and nebivolol (–13%); (P<0.05 for each group). There was not a statistical significance observed between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
on day 1, then 25 mg BID vs nebivolol 10 mg on day 1, then 5 mg QD				Compared to baseline, heart rate at exercise was decreased at 24 hours after the respective last dose at the end of 1 week of chronic administration by bisoprolol (–14%), carvedilol (12 hours; –15%) and nebivolol (–13%); (P<0.05 in all cases). There was not a statistical significance observed between the groups. All of the agents significantly decreased SBP both at rest and exercise at 3 and 24 h after the first dose as well at 24 h after the last dose after 7 days of chronic administration (P<0.05 in all cases). None of the agents had a significant effect on DBP at rest or at exercise. Secondary: Compared to placebo, nocturnal melatonin release was decreased by bisoprolol (–44%, P<0.05) whereas nebivolol (-16%) and carvedilol (–19%) had no effect. Total QOL with carvedilol (8.0±0.8) was slightly but significantly lower than that with placebo (8.6±0.4), nebivolol (8.5±0.6) and bisoprolol (8.4±0.5); (P<0.05 in all cases).
Lewin et al.[29] (1993) Bisoprolol 5 mg and HCTZ 6.25 mg QD (fixed-dose combination) vs placebo	MC, PC Adult patients with stable mild to moderate (sitting DBP 95 to 114 mm Hg) essential hypertension	N=36 4 weeks	Primary: Changes in 24-hour ambulatory daytime and nighttime blood pressure	Primary: There were statistically significant reductions in blood pressure and pulse (P<0.01) at weeks 2 and 4 of treatment. There were statistically significant reductions (P<0.01) in 24 hour SBP and DBP, daytime and nighttime blood pressure, compared to the end of the placebo phase. There was a reduction in systolic and diastolic load also (P<0.01). The combination was well tolerated. The scores from the overall quality-of-life questionnaire indicated an improvement with the combination (P=0.02).
Benetos et al.[31] (2000) Bisoprolol 2.5 mg and HCTZ 6.25	DB, MC, PG, RCT Patients over 60 years with supine SBP 160 to 210 mm	N=164 12 weeks	Primary: Changes in blood pressure, heart rate, adverse events and QOL scores	Primary: Both bisoprolol-HCTZ and amlodipine significantly reduced SBP (–20.0±13.7 and –19.6±14.2 mm Hg, respectively; P<0.001) and DBP (–4.5±7.4 and –2.4±8.4 mm Hg, respectively from baseline to week 12, but there was not a significant difference between the agents (SBP; P=0.85

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD (fixed-dose combination) vs amlodipine 5 mg QD	Hg and DBP <90 mm Hg			and DBP; P=0.09). Bisoprolol-HCTZ significantly reduced heart rate from baseline, but amlodipine did not (–7.6±8.4 beats/min [P<0.001] and –0.2±11.4 beats/min, respectively). Bisoprolol-HCTZ significantly reduced heart rate when compared to amlodipine (P=0.0001). Overall adverse events were not significantly different between the amlodipine and the bisoprolol-HCTZ group (39% and 40%, respectively). Adverse events reported included headache, leg edema, fatigue and bradycardia but severity of events was not reported. Overall QOL scores were not significantly different between the amlodipine and the bisoprolol-HCTZ group.
Prisant et al.[39] (1995) Bisoprolol 2.5 mg-HCTZ 6.25 mg, bisoprolol 5 mg-HCTZ 6.25 mg, or bisoprolol 10 mg-HCTZ 6.25 mg vs enalapril 5, 10, or 20 mg vs amlodipine 2.5, 5, or 10 mg	DB, MC, PG, RCT Patients ≥21 years with mild to moderate essential hypertension, (average sitting DBP 95 to 114 mm Hg) each treatment was once daily and titrated to effect	N=218 17 weeks	Primary: Mean change from baseline in SBP and DBP, lab measurements, adverse events and QOL questionnaire	Primary: Mean decreases in SBP and DBP from baseline were 13.4/10.7 mm Hg for bisoprolol-HCTZ combination patients, 12.8/10.2 mm Hg for amlodipine patients, and 7.3/6.6 mm Hg for enalapril patients. The hypotensive effects were significant for all three groups (P<0.001). SBP and DBP mean changes from baseline for the bisoprolol-HCTZ combination group and the amlodipine group were greater than the change from baseline for the enalapril group (P<0.01). Response rates (DBP ≤90 mm Hg or ≥10 mm Hg decrease from baseline) were 71% for the bisoprolol-HCTZ combination group, 69% for the amlodipine group, and 45% for the enalapril group. The response rates for the bisoprolol-HCTZ combination and the amlodipine groups differed significantly from the enalapril group (P<0.01). 29% of bisoprolol patients had adverse experiences compared to 42% of amlodipine patients (P=0.12). Nearly 47% of enalapril patients had adverse experience compared to bisoprolol (P=0.04). Adverse events reported included headache, fatigue, peripheral edema and dizziness.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Drug related adverse events were 16% for the bisoprolol-HCTZ patients, 21% for the amlodipine patients, and 23% for the enalapril patients. There was no significant difference between the groups. Enalapril demonstrated a mean decrease from baseline of 7.9 mg/dL for total cholesterol (P=0.02 vs amlodipine) and 6.6 mg/dL for low-density lipoprotein cholesterol (P=0.04 vs amlodipine) which were not significantly different from the increase from the bisoprolol-HCTZ group of 1.7 mg/dL (P=0.07 vs enalapril) for total cholesterol and +0.6 mg/dL in low-density lipoprotein cholesterol. However, the increase in triglycerides was highest for bisoprolol-HCTZ-treated patients compared with amlodipine- and enalapril treated patients (P=0.08, for bisoprolol-HCTZ vs enalapril). There was not a significant difference from baseline or between treatment groups in quality-of-life scores: +0.9 or the bisoprolol-HCTZ group, +0.5 (1.2) for the amlodipine group and 2.3 for the enalapril group.
Frishman et al.[33] (1994) Bisoprolol 2, 5, 10, or 40 mg QD vs HCTZ 6.25 or 25 mg once daily vs bisoprolol plus HCTZ, all possible combinations	DB, MC, PC, RCT Patients 21 years and older with mild to moderate essential hypertension whose weight was 35% of the ideal for height and frame and mean sitting DBP was stable and between 95 to 115 mm Hg	N=512 12 weeks	Primary: Changes in DBP and SBP	Primary: All treatment groups (all doses) of bisoprolol, HCTZ and the combination of bisoprolol-HCTZ significantly reduced sitting DBP from baseline (P<0.01). The reduction in blood pressure was significantly greater as the doses of the bisoprolol, HCTZ and the combination of bisoprolol-HCTZ were increased (P<0.05). The combination bisoprolol-HCTZ significantly reduced sitting DBP compared to the separate agents as monotherapy (P<0.01). With higher doses of HCTZ, there was a significantly higher incidence of hypokalemia, defined as potassium <3.5 mmol/L (P<0.01). Incidence of hyperuricemia also significantly increased with the increase in HCTZ dose (P<0.01). Adverse events associated with hypokalemia and hyperuricemia were not reported. As the dose of bisoprolol was increased, the frequency and severity of adverse events reported significantly increased (P<0.05). Adverse events

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported included asthenia, diarrhea, dyspepsia and somnolence, but severity of effects was not reported.
Frishman et al.[34] (1995) Bisoprolol 5 mg QD vs HCTZ 25 mg QD vs bisoprolol 5 mg-HCTZ 6.25 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥21 years with mild to moderate (stage II or II) systemic hypertension whose body weight was not >10% below or 35% above the ideal weight for height and frame, and were off all antihypertensive medications before study entry and sitting DBP was 95 to 115 mm Hg on 3 consecutive weekly visits	N=547 10 weeks	Primary: Changes in blood pressure and adverse events	Primary: All active treatment groups significantly reduced sitting DBP and SBP from baseline compared to placebo (P<0.01). Addition of HCTZ 6.25 mg contributed significantly to the blood pressure lowering effects of bisoprolol 5 mg. The combination bisoprolol 5 mg-HCTZ 6.25 mg produced a significantly greater reduction in mean sitting DBP from baseline (-12.6±0.5 mm Hg) than bisoprolol 5 mg alone (-10.5±0.5 mm Hg; P=0.02) and HCTZ 25 mg alone (-8.5±0.5 mm Hg; P<0.01). Bisoprolol 5 mg monotherapy was significantly better a reducing DBP compared to HCTZ 25 mg alone (P=0.03). The combination bisoprolol 5 mg-HCTZ 6.25 mg produced a significantly greater reduction in mean sitting SBP from baseline (-15.8 mm Hg) than bisoprolol 5 mg alone (-10 mm Hg; P<0.01) and HCTZ 25 mg alone (-15.8 mm Hg; P<0.01). There was not a significant difference in mean reduction between bisoprolol 5 mg alone and HCTZ 25 mg alone. Bisoprolol 5 mg and HCTZ 6.25 mg in combination had a 73% response rate compared to 61% for the bisoprolol group and 47% for the HCTZ group. Bisoprolol 5 mg and HCTZ 6.25 mg in combination was found to be significantly more effective than bisoprolol 5 mg or HCTZ 25 mg in all subgroups of patients regardless of age, race, gender, or smoking history (P>0.05 for all comparisons). Bisoprolol 5 mg and HCTZ 6.25 mg in combination did not have an increase in frequency or severity of adverse events. The adverse events were comparable to that in the placebo group and frequency among groups was not significant. The most common adverse events reported were headache, dizziness, fatigue and cough.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significantly greater number patients in the HCTZ 25 mg group (6.5%) experienced hypokalemia (potassium <3.4 mEq/L) compared to the bisoprolol 5 mg group (0.7%; P<0.01), the bisoprolol-HCTZ group (0.7%; P<0.01) and placebo (0%; P<0.01). Hyperglycemia occurred in 7.4% of patients in the HCTZ 25 mg group, which was significantly higher then in the placebo group (5.2%; P=0.03). Also, the incidence of hyperuricemia (uric acid >7.5 mg/dL) was significantly higher in the HCTZ 25 mg group (24.4%) compared to placebo (2.7%; P<0.01).
Hamaad et al.[111] (2007) Carvedilol 3.125 to 25 mg BID vs bisoprolol 1.25 to 10 mg QD	RCT Patients with stable LVEF of <40% and treated with diuretic and ACE inhibitor or ARB	N=31 12 weeks	Primary: Blood pressure, heart rate responses and both time and frequency domain heart rate variability	Primary: Carvedilol significantly reduced DBP from baseline to week 12 of therapy (stage 6), but bisoprolol did not: 10±16 mm Hg (P=0.045) and 7±16 mm Hg, respectively (P=0.159), but there was not a significant difference between groups. Both carvedilol and bisoprolol significantly reduced SBP from baseline to week 12 of therapy (stage 6): 18±28 mm Hg (P=0.045) and 12±16 mm Hg, respectively (P<0.003) but there was not a significant difference between groups. Both carvedilol and bisoprolol significantly decreased mean heart rate from baseline to week 12 of therapy (stage 6): 25±20 bpm and 23±10 bpm, respectively (P<0.01 for both agents vs baseline) but there was not a significant difference between groups (P=0.708). Neither carvedilol nor bisoprolol significantly increased 4 of the 5 heart rate variability indices measured including SDNN, RMSSD, low frequency power or high frequency power. But both carvedilol and bisoprolol significantly increased TI from baseline to week 12 of therapy (stage 6): 7±6 (P<0.01) and 5±6 (P=0.01), respectively, but there was not a significant difference between groups.
Saunders et al.[83] (1987) Labetalol 100 to 800 mg BID	DB, PG Patients with mild to moderate hypertension	N=153 Duration not specified	Primary: Blood pressure and heart rate	Primary: Labetalol was significantly better than propranolol at the end of monotherapy at lowering DBP (P<0.05) but there was no difference in lowering SBP.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs propranolol 40 to 320 mg				Propranolol was significantly better at lowering heart rate compared to labetalol (P<0.01). No difference in the decrease in blood pressure after a diuretic was added.
Dafgard et al.[32] (1981) Metoprolol 200 mg-HCTZ 25 mg QAM or HCTZ 50 mg QAM vs HCTZ 25 mg QAM	DB, MC, RCT Patients with essential hypertension (WHO stages I or II) not adequately controlled (≥160/95 mm Hg) on HCTZ 25 mg/day	N=31 32 weeks	Primary: Blood pressure, heart rate, adverse events and laboratory values	Primary: After the 8 week run-in period with HCTZ 25 mg alone, the mean supine blood pressure was significantly reduced from 183/110 to 172/103 mm Hg (P<0.01/P<0.01). The increased dose of HCTZ 50 mg following the run-in period did not further significantly reduce the mean blood pressure (165/104 mm Hg). A small but statistically significant reduction in supine heart rate was seen when the HCTZ dose was increased from 25 to 50 mg (82 down to 78 beats/min; P<0.05). After the 12 week double-blind period, the mean supine blood pressure was 153/98 mm Hg in the HCTZ 50 mg group. After the 12 week follow-up period, there was not any additional decrease in blood pressure (153/97 mm Hg). Combination product of metoprolol and HCTZ produced a significant reduction in supine blood pressure after 12 weeks of therapy from 172/105 mm Hg on HCTZ 25 mg alone to 154/97 mm Hg on the combination therapy (P<0.001/P<0.01). Similar results were found with the standing blood pressure reductions, from 165/108 to 147/97 mm Hg (P<0.001/P<0.001). After the 8 week run-in period, the supine heart rate was 80 beats/min which decreased to 64 beats/min with the metoprolol-HCTZ combination (P<0.001). The values for standing heart rate demonstrated similar significant reductions (85 to 66 beats/min; P<0.001). After the additional 12 week follow-up, the patients in the metoprolol-HCTZ combination group did not demonstrate a significant further reduction in heart rate or blood pressure in any position.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both agents were tolerated and the most common adverse events reported included insomnia, headache, tiredness, and shortness of breath. A majority of event s were mild, few were moderate and none were severe. The only significant changes in laboratory values occurred with the HCTZ 25 mg and 50 mg groups, where an increase in serum uric acid was observed from 0.30 to 0.34 and 0.35 mmol/L, respectively; P<0.01 and P<0.05; respectively).
Smilde et al.[40] (1983) Metoprolol 400 mg QAM for 5 weeks, then metoprolol 200 mg-HCTZ 25 mg QAM for 5 weeks (Group 1) vs metoprolol 200 mg-HCTZ 25 mg QAM for 5 weeks, then metoprolol 400 mg QAM for 5 weeks	DB, PG, RCT, XO Patients <65 years with essential hypertension (supine DBP ≥95 mm Hg) not controlled on metoprolol 200 mg alone	N=37 15 weeks	Primary: Changes in DBP, SBP and heart rate	Primary: Both group 1 and 2 significantly reduced DBP (P<0.01) from baseline and the two groups were not significantly different from each other. The combination products significantly reduced SBP from baseline (P<0.05, P<0.01 depending on comparison) Group 2 significantly reduced heart arte at the end of the study compared to baseline (P<0.05). Clinically relevant changes in laboratory parameters or mean body weight were not observed between the groups.
Liedholm et al.[37] (1981) Metoprolol 100 mg-HCTZ 12.5 mg BID (Group A) vs metoprolol 100 mg-HCTZ 25 mg	RCT Patients 18-72 years with mild to moderate essential hypertension (WHO I or II) <u>Extended Study:</u> OL	N=55 12 weeks <u>Extended Study:</u> N=49 6 months	Primary: Change in blood pressure <u>Extended Study:</u> Primary: Change in blood pressure	Primary: In Group A, there was a significant decrease in supine blood pressure from 189/112 to 172/105 mm Hg with metoprolol monotherapy and further reduction to 148/92 mm Hg with the metoprolol 100 mg-HCTZ 12.5 mg combination group (P<0.001/P<0.001). In Group B, there was a significant decrease in supine blood pressure from 184/111 to 170/104 mm Hg with metoprolol monotherapy and further reduced to 152/96 mm Hg with metoprolol 100 mg-HCTZ 25 mg combination group (P<0.01/P<0.05) after 12 weeks.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID (Group B) Extended Study: metoprolol 100 mg-HCTZ 12.5 mg, 2 tablets QAM	Those patients who participated in the initial trial, had poor blood pressure control on existing antihypertensive therapy, and were being treated with a β-blocker and additional diuretic therapy			Supine heart rate fell in Group A from 78 to 68 beats/min with metoprolol monotherapy (P<0.001). No further heart rate reduction was noted with the metoprolol 100 mg-HCTZ 12.5 mg. In Group B, supine heart rate fell from 76 to 69 beats/min (P<0.05). No further heart rate reduction was seen with metoprolol 100 mg-HCTZ 25 mg. In Group A, serum sodium fell from 143 to 140 mmol/L (P<0.01). In Group B, serum potassium fell with from 4.4 to 4.0 mmol/L (P<0.001). Extended Study: Primary: After six months of extended the therapy, there was no further significant reductions in supine or standing blood pressure, but there was a reduction in standing DBP from 97 to 95 mm Hg (P<0.05).
Rosei et al.[78] (2003) Nebivolol 5 mg QD vs lisinopril 20 mg QD	DB, MC, PG, RCT Patients between 24 and 65 years with mild to moderate uncomplicated essential hypertension that was newly diagnosed, or previous antihypertensive therapy was withdrawn at >1 month before active treatment, and had a sitting DBP of >95 and <114 mm Hg.	N=65 12 weeks	Primary: Response rates and changes in sitting blood pressure Secondary: Standing blood pressure and sitting and standing heart rate	Primary: There was not a significant difference in response rates observed between the two treatment groups. Both treatment groups significantly reduced sitting SBP (P<0.0001) and DBP (P<0.0001) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week 8, DBP was significantly lower in the nebivolol group compared to the lisinopril group (P<0.05). Secondary: There was not a significant difference observed between treatment groups in standing blood pressure measurements. Both treatment groups significantly reduced sitting heart rate (P<0.01) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week 8, heart rate were significantly lower in the nebivolol group compared to the lisinopril group (P<0.05).
Mazza et al.[76] (2002) Nebivolol 2.5 to 5	DB, MC, PG, RCT Patients between 65-89 years of age	N=168 16 weeks	Primary: Changes of sitting blood pressure and response rates	Primary: There was not a significant difference observed between the amlodipine and nebivolol treatments groups in changes in sitting DBP (blood pressure values and P values not reported). At weeks 4 and 8, a slightly lower

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD vs amlodipine 5 to 10 mg QD	with mild to moderate essential hypertension and DBP ranging from 95-114 mm Hg		Secondary: Standing blood pressure changes, and standing and sitting heart rate changes	sitting SBP was observed in per-protocol patients in the amlodipine groups vs those in the nebivolol group (blood pressure values not reported, P<0.005). Response rates were not significantly difference between the amlodipine group and the nebivolol group (86% vs 88%, respectively). The percentage of patients who reached normalization (blood pressure <140/90 mm Hg) was no significant between the amlodipine and the nebivolol groups (47% vs 50%). Secondary: There were significant differences in standing blood pressure observed between the groups; with the exception of S blood pressure which was lower in the amlodipine group at week 8. Heart rate was significantly lower in the nebivolol group compared to the amlodipine group at all treatment visits (P<0.001). Patients in the amlodipine group experienced a significantly greater rate of headache (7 vs 5 patients) and ankle edema (12 vs 0 patients) compared to the patients in the nebivolol group (P<0.05 for both).
Van Bortel et al.[79] (2005) Nebivolol 5 mg QD vs losartan 50 mg QD If after 6 weeks, DBP was not normalized, then HCTZ 12.5 mg QD was added to therapy	DB, MC, PG, RCT Patients less than 70 years of age with DBP at randomization between 95 and 114 mm Hg	314 12 weeks	Primary: Effects on blood pressure and overall QOL Secondary: Comparison of different aspects of QOL	Primary: At the end of 12 weeks, both nebivolol and losartan significantly reduced SBP compared to baseline (P<0.0001 for both), but the agents were not significantly different from each other. Both agents also significantly decreased DBP compared to baseline (P<0.0001), but nebivolol significantly reduced DBP compared to losartan (P<0.02). At the end of 12 weeks, both nebivolol and losartan significantly improved QOL scores compared to baseline (P<0.007), but the agents were not significantly different from each other. Secondary: At week 12 there was not a significant difference observed in the individual questions of the QOL questionnaire between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Questions inquired about headaches, lightheadedness, sleepiness, flushing, and sexual function.
Van Bortel et al.[90] (2008) Nebivolol vs active comparator (ARB, β-blocker, CCB, or ACE inhibitor) or placebo	MA Patients with essential hypertension	N=2,653 (12 trials) Varied among studies	Primary: Antihypertensive effect and tolerability	Primary: Overall, higher response rates were observed with nebivolol than all the other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001) but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), CCBs (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized blood pressure with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage of patient taking nebivolol obtained normalized blood pressure compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004), and CCBs (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the groups individually, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and CCBs (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08; P=0.127).
Veterans Administration Cooperative Study Group on Antihypertensive Agents[42] (1983) Nadolol 80 to 240 mg QAM	DB, RCT Men 20-69 years with pretreatment DBP of 95 to 114 mm Hg	N=365 12 weeks	Primary: Changes in blood pressure, change in blood pressure among races, heart rate, adverse events and laboratory values	Primary: DBP of <90 mm Hg was achieved in 49% of the nadolol patients, 46% of the bendroflumethiazide patients, and 85% of the combination patients. There was a significantly higher percentage of patients who achieved the DBP goal compared to the nadolol alone group and bendroflumethiazide group alone (P<0.01 for both). The reduction in SBP was significantly greater in the combination group compared to the nadolol alone and bendroflumethiazide group (-25.3±1.4, -10.5±1.6, and -17.4±1.7 mm Hg, respectively; P<0.001 for both) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs bendro-flumethiazide 5 to 10 mg* QAM vs nadolol and bendro-flumethiazide				bendroflumethiazide produced a significantly greater reduction compared to nadolol alone (P<0.01). The reduction of DBP in white patients was significantly greater then the decrease in African American (decrease of 15.6 vs 9.6 mm Hg, respectively; P<0.001). In addition, 77% of white patients achieved DBP of <90 mm Hg compared to only 31% of African American patients (P<0.001). Adverse events were infrequent. The most common were impotence, lethargy, weakness and postural dizziness, which occurred more often with bendroflumethiazide than nadolol. Significant reductions in average heart rate from baseline were observed with nadolol alone (decrease by 16.1 beats/min; P<0.001) and with the combination product (decrease by15.8 beats/min; P<0.001). Serum potassium levels significantly decreased from baseline in the bendroflumethiazide group by -0.57±0.06 mEq/L (P<0.001) and in the combination group by -0.44±0.05 mEq/L (P<0.001). Serum uric acid levels significantly increased from baseline in the bendroflumethiazide group by 1.7±0.2 mg/dL (P<0.001), in the nadolol group by 0.4±0.1 mg/dL (P<0.01) and in the combination group by -1.9±0.1 mg/dL (P<0.001). Fasting glucose levels significantly increased from baseline in the bendroflumethiazide group by 6.1±2.1 mg/dL (P<0.001) and in the combination group by 7.4±1.1 mg/dL (P<0.001). Cholesterol significantly increased from baseline in the bendroflumethiazide group by 11.5±4.3 mg/dL (P<0.001). Triglycerides significantly increased from baseline in the bendroflumethiazide group by 34.6±14.8 mg/dL (P<0.01), in the nadolol group by 38.7±13.2 mg/dL (P<0.01) and in the combination group by 67.8±11.9 mg/dL (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Frick et al.[80] (1978) Penbutolol 40 mg BID vs propranolol 160 mg BID	DB, XO Patients 29-64 years of age with hypertension	N=20 13 weeks	Primary: Blood pressure and heart rate	Primary: Penbutolol significantly reduced supine and standing blood pressures (both SBP and DBP) from baseline (P<0.05). Propranolol also significantly reduced blood pressures from baseline (SBP: P<0.02 and diastolic: P<0.01), but there was not significant difference between agents. Penbutolol significantly reduced supine and standing heart rates from baseline (from 76±10 to 61±9; P<0.001 and from 85±13 to 67±8; P<0.001, respectively. Propranolol also significantly reduced heart rates from baseline (to 59±8; P<0.001 and to 63±7; P<0.001, respectively), but there was not significant difference between agents.
VA Cooperative Study[85] (1977) <u>Propaserp group</u>: Propranolol 40-160 mg TID (P), propranolol 40-160 mg TID plus HCTZ 35 mg (P+T), propranolol 40-160 mg TID plus hydralazine 35 mg (P+H) or propranolol 40-160 mg TID plus HCTZ 35 mg plus hydralazine 35 mg (P+T+H) vs <u>Hydrazide group</u>: Reserpine 35 mg plus HCTZ 35 mg (R+T)	DB, RCT Men 18-59 years with DBP of 90-114 mm Hg	N=450 18 months	Primary: Percent of patients who achieved a DBP <90 mm Hg at 6 months, heart rate and withdrawal rate	Primary: At 6 months, significantly more patients in the R+T arm (88%) attained a DBP <90 mm Hg and at least 5 mm Hg less than the initial blood pressure compared to the P arm (52%; P<0.01) and the P+H arm (72%; P<0.05). The other arms: P+T (81%) and P+T+H (92%) were not significantly different than the R+T arm. The 12 and 18 month results do not have the statistical validity of the 6 month results due to the reduced sample size. The following percentage of patients attained DBP <90 mm Hg and at least 5 mm Hg less than the initial pressure: R+T=89.1% and 82.6%, P=59.5 and 58.1%, P+T=86.0 and 86.4%, P+H=67.4 and 76.1%, and P+T+H=89.4 and 91.8%. There was not a significance difference in heart rate reductions at 6 months and 18 months between the groups (R+T=5.0±1.3 and 5.0±1.3 mean change in heart rate, P=9.1±1.3 and 9.2±1.8, P+T=8.8±1.2 and 6.3±1.5, P+H=8.9±1.3 and 7.8±1.5, and P+T+H=5.9±1.1 and 7.7±1.5). Withdrawals for any reason were similar between the treatment arms and were not statistically significant (R+T=14 patients, P=11, P+T=12, P+H=14, and P+T+H=16).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stevens et al.[41] (1982) Dose-finding phase: Propranolol 80, 160, 240, or 320 mg/day in 2 divided doses vs propranolol 80 mg-HCTZ 50 mg, propranolol 160 mg-HCTZ 50 mg, propranolol 240 mg-HCTZ 50 mg, or propranolol 320 mg-HCTZ 50 mg/day in 2 divided doses Double-blind phase: combination propranolol-HCTZ vs propranolol vs HCTZ	DB, PG, RCT Patients with mild to moderate essential hypertension (DBP 100 to 125 mm Hg)	N=158 25 weeks	Primary: Mean changes of SBP and DB, heart rate, lab values	Primary: After the 12 week dose finding-phase, 94% of patients had a decrease greater than or equal to 10 mm Hg in DBP. The mean SBP and DBP reduced from 158.0 (±17.3)/105.6 (±6.0) mm Hg to 131.5 (±14.4)/86.4 (± 6.7) mm Hg (P<0.001). After the 10 week portion of the study, there were significantly greater increases (P<0.05) in mean SBP or DBP with propranolol and HCTZ alone vs the combination product of propranolol-HCTZ from the end of the dose-finding to the last four biweekly visits to the mean of those visits, and to the last visit. The mean increases of SBP and DBP at the endpoint were: propranolol, 10.2/6.3 mm Hg; HCTZ 13.1/9.3 mm Hg; propranolol-HCTZ combination product 3/1.5 mm Hg. There was a significant decrease in heart rate as the dose of propranolol was increased thought the trial (P>0.30). The only lab value that showed a statistically significant change was serum chloride. The percent of patients that fell outside of the normal range were as follows: propranolol 6/36 (17%), HCTZ 14/37 (38%), and combination 4/28 (14%); P<0.05.
de Leeuw et al.[30] (1997)	DB, MC, PC, RCT	N=205	Primary: Changes in supine	Primary: Each of the three active treatments was significantly more effective than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Active treatment group: verapamil SR 180 mg-trandolapril 2 mg, atenolol 100 mg-chlorthalidone 25 mg or lisinopril 20 mg-HCTZ 12.5 mg vs placebo There was a single-blind placebo 4-week run in period.	Patients 18-70 years with essential hypertension (WHO I or II) newly or unsuccessfully treated, with supine DBP 101 to 114 mm Hg in week 4 of the run-in period	12 weeks	blood pressure, standing blood pressure response rates, and normalization rates	placebo in reducing in DBP in seated patients. Changes in DBP were as follows: verapamil SR-trandolapril: –13 (95% CI, –16 to –9), atenolol-chlorthalidone –13 (95% CI, –16 to –9), lisinopril-HCTZ –12 (95% CI, –15 to –9) and placebo: –3 (95% CI, –7 to 0); P=0.0001 for all groups compared to placebo, but there was not a statistical significance among treatment groups. Each of the three active treatments was significantly more effective than placebo in reducing SBP in seated patients. Changes in SBP were as follows: verapamil SR-trandolapril: –27 (95% CI, –33 to –21), atenolol-chlorthalidone –28 (95% CI, –34 to –22), lisinopril-HCTZ –23 (95% CI, –29 to –17) and placebo: –3 (95% CI, –9 to +3); P=0.0001 for all groups compared to placebo, but there was not a statistical significance among treatment groups. Effects on standing blood pressure demonstrated similar results as the effects on sitting blood pressure). Normalization of DBP (<90 mm Hg), corrected for placebo, were significantly higher in the treatment groups compared to the placebo group: 33% (95% CI, 16% to 50%; P<0.0005) of patients in the verapamil SR-trandolapril group, 31% (95% CI, 14% to 48%; P<0.002) of patients in the atenolol-chlorthalidone group and 25% (95% CI, 9% to 42%; P<0.005) of patients in the lisinopril-HCTZ group. Response rates were significantly higher in the treatment groups compared to placebo: 40% (95% CI, 22% to 58%; P<0.0001) patients in verapamil SR-trandolapril group, 44% (95% CI, 27% to 61%; P<0.0001) of patients in the atenolol-chlorthalidone group, and 37% (95% CI, 19% to 55%; P<0.0002) of patients in the lisinopril-HCTZ group.
Post Myocardial Infarction and Other Cardiovascular Outcomes Trials				
Gottlieb et al.[126] (2001) Atenolol vs	RETRO Patients discharged from the hospital with the diagnosis of an acute	N=69,338 2 years	Primary: Mortality rates at one year and two years	Primary: β-blockers demonstrated an 40% overall reduction in mortality compared to those patient who did not receive β-blocker therapy. One year mortality rates in the three groups were metoprolol 8.32% (CI, 8.07 to 8.58, atenolol 8.16% (CI, 7.76 to 8.58), propranolol 9.55% (CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metoprolol vs propranolol vs other (not specified)	myocardial infarction and on a β-blocker			9.69 to 10.48), and other 9.19% (CI, 8.16 to 10.33),. Two-year mortality rates in the three groups were metoprolol 13.52% (CI, 13.21 to 13.84), atenolol 13.41% (CI, 12.91 to 13.93), propranolol 15.91% (CI, 14.83 to 17.05), and other 15.17% (CI, 13.88 to 16.56). There were no differences between atenolol and metoprolol at the end of the 2 years, both of which were statistically better than propranolol. Compared with metoprolol, patients discharged on propranolol had 15% increased mortality at 1 year and an 18% increased mortality at 2 years, which were significantly higher than metoprolol.
Black et al.[86] (2003) CONVINCE Atenolol 50 mg or HCTZ 12.5 mg QD vs COER verapamil 180 mg QD	DB, MC, RCT Patients ≥55 years with at least 1 other established risk factor for cardiovascular, in addition to hypertension	N=16,602 3 years	Primary: Acute myocardial infarction, stroke, or cardiovascular disease-related death Secondary: Expanded cardiovascular disease, all-cause mortality, cancer, hospitalization for bleeding, incidence of primary end points occurring between 6 AM and noon	Primary: There was not a statistically significant difference observed in the occurrence of myocardial infarctions (133 vs 166 patients, respectively; HR, 0.82; 95% CI, 0.65 to 1.03; P=0.09), fatal or nonfatal stroke (133 vs 118 patients, respectively; HR, 1.15; 95% CI, 0.90 to 1.48; P=0.26) or cardiovascular disease-related death, (152 vs 143, respectively; HR, 1.09; 95% CI, 0.87 to 1.37; P=0.47) between the COER verapamil group and the active control group. Secondary: There was not a statistically significant difference observed in the occurrence of expanded cardiovascular diseases (793 vs 775 patients, respectively; HR, 1.05; 95% CI, 0.95 to 1.16; P=0.31), all-cause mortality (337 vs 319 patients, respectively; HR, 1.08; 95% CI, 0.93 to 1.26; P=0.32), cancer (310 vs 299, respectively; HR, 1.06; 95% CI, 0.91 to 1.24; P=0.46), or in incidence of primary endpoints occurring between 6 AM and noon (99 vs 88, respectively; HR, 1.15; 95% CI, 0.86 to 1.53; P=0.34) between the COER verapamil group and the active control group. There was a statistically significant difference in occurrence of hospitalizations for bleeding (118 vs 79 patients, respectively; HR, 1.51; 95% CI, 1.15 to 2.04; P=0.003), between the COER verapamil group and the active control group.
Hannson et al.[88] (1999)	BE, MC, OL, RCT Swedish men and	N=6,614 60 months	Primary: Combined fatal stroke, myocardial	Primary: The combined fatal mortality endpoints occurred in 221of the 2,213 patients in the conventional drugs group and in 438 of 4,401 in the newer

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
STOP-2 Conventional drug group Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs Newer drug group ACE inhibitors: enalapril 10 mg QD or lisinopril 10 mg QD or calcium antagonists: felodipine 2.5 mg QD, or isradipine 2-5 mg QD	women between 70-84 years old with treated or untreated essential with hypertension on 3 separate occasions defined by systolic pressure ≥180 mm Hg, diastolic pressure >105 mm Hg, or both		infarction and other fatal cardiovascular disease, and combined fatal and nonfatal stroke, myocardial infarction and other cardiovascular mortality	drugs group (RR, 0.99; 95% CI, 0.84 to 1.16; P=0.89). The combined fatal and nonfatal mortality endpoints occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (RR, 0.96; 95% CI, 0.86 to 1.08; P=0.49).
Iliuta et al.[139] (2009) Betaxolol 20mg daily vs metoprolol 100mg twice daily	OL, MC Patients who were admitted for CABG surgery	N=1352 30 days	Primary: Mortality, in-hospital occurrence of atrial fibrillation, total hospital stay and immobilization (days)	Primary: Betaxolol significantly decreased 30-day mortality (P=0.001) and in-hospital atrial fibrillation (P=0.0001) compared to metoprolol. Patients taking betaxolol were less likely to be hospitalized for >15 days (9.94 vs 13.27, P=0.01) or immobilized for >3 days (5.19 vs 8.26, p=0.002) compared to metoprolol.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Jonsson et al.[125] (2005) Carvedilol 6.25 to 25 mg BID vs atenolol 12.5 to 50 mg BID	OL, R Patients between 18 to 80 years of age with chest pain consistent with an acute myocardial infarction, admitted to the hospital 24 hours after onset and a confirmed diagnosis with significant increase in cardiac enzymes	N=232 1.5±1.3 years	Primary: Change in global or regional LVEF after 12 months, cardiovascular endpoints and adverse events	Primary: At baseline, mean global LVEF was 54.8% in the carvedilol and 53.0% in the atenolol group and increased after 12 months to 57.1% in the carvedilol and 56.0% in the atenolol group. There was not a significant difference between treatment groups for change in global or regional LVEF (values were not reported),. There was not a significant difference in the rates of occurrence of the first serious cardiovascular events observed between the carvedilol and atenolol groups after adjustment for diuretic use (0.247 vs 0.299; RR, 0.83; 95% CI, 0.56 to 1.23; P=0.39). Of the nonserious adverse events reported, a greater incidence of colds hand and feet were reported in the atenolol group (38 [33.3%]) compared to the carvedilol group (24 [20%]; P=0.025).
Olsson et al.[124] (1992) Metoprolol 100 mg BID vs placebo	MA Patients with a past history of myocardial infarction	N=5,474 (5 trials) 3 months to 3 years	Primary: All-cause mortality and sudden deaths	Primary: Metoprolol significantly reduced all-cause mortality compared to placebo (188 vs 223 deaths; P=0.036). Metoprolol significantly reduced sudden deaths compared to placebo (62 vs 104 deaths; P=0.002).
Hannson et al.[87] (2000) NORDIL β-blocker, diuretic, or both vs diltiazem 180 to 360 mg QD	BE, MC, OL, RCT Patients 50-74 with DBP of ≥100 mm Hg	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, myocardial infarction and other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal	Primary: There was not a statistically significant difference observed in the occurrence of the combined primary endpoint between the diltiazem group compared to the conventional group (403 vs 400 patients, respectively; RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: There were significantly fewer occurrences of fatal plus nonfatal stroke in the diltiazem group (159 patients) compared to the conventional group (196 patients; RR, 0.80; 95% CI, 0.65 to 0.99; P=0·04). There was not statistically significant difference observed in the occurrence of fatal plus nonfatal myocardial infarctions between the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			myocardial infarction	diltiazem group and the conventional group (183 vs 157 patients, respectively; RR, 1.16; 95% CI, 0.94 to 1.44; P=0.17).
Messerli et al.[89] (1998) β-blockers (atenolol, metoprolol, pindolol) vs diuretics (amiloride, chlorthalidone, HCTZ, HCTZ-triamterene or thiazide)	MA Patients ≥60 years with hypertension	N=16,164 (10 trials) 1 year	Primary: Cardiovascular morbidity and mortality and all-cause morbidity	Primary: Diuretic treatment significantly reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64 to 0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78 to 1.23). Diuretic treatment significantly reduced the odds for all-cause mortality by 14% (OR, 0.86; 95% CI, 0.77 to 0.96) while β-blockers did not reduce all-cause mortality (OR, 1.05; 95% CI, 0.88 to 1.25).
Wiysonge et al.[91] (2007) β-blocker therapy (atenolol, metoprolol, oxprenolol, propranolol) vs other antihypertensive therapies (i.e., placebo, diuretic, calcium-channel blocker, or renin-angiotensin system inhibitors)	MA Patients ≥18 years of age with hypertension	N=91,561 (13 trials) Variable duration	Primary: All cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, and adverse drug reactions	Primary: There was not a statistically significant difference observed in all cause mortality between the β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19), and RAS inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24). There was a statistically significant higher rate in all cause mortality with β-blocker therapy compared to CCB therapy (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a statistically significant decrease in stroke seen with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a statistically significant increase in stroke with β-blocker therapy compared to CCBs (RR, 1.24; 95% CI, 1.11 to 1.40) and RAS inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53], but there was no difference found compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blockers and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), a diuretic (RR, 1.12; 95% CI, 0.82 to 1.54), a CCB (RR, 1.05; 95% CI, 0.96 to 1.15), or an RAS inhibitor (RR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97]. The effect of β-blockers on cardiovascular disease was significantly worse than that of CCBs (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28), or RAS inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a statistically significant higher rate of discontinuation of therapy due to side effects with β-blocker compared to those on diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and RAS inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference with CCBs (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Lindholm et al.[92] (2005) β-blockers (atenolol, metoprolol, oxprenolol, pindolol, propranolol) vs other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide, captopril, diltiazem, enalapril, felodipine, HCTZ,	MA Patients with primary hypertension receiving treatment with a β-blocker as first-line therapy	N=105,951 (13 trials) 2.1-10 years	Primary: Stroke, myocardial infarction and all-cause mortality	Primary: The relative risk of stroke was 16% higher for β-blockers than for the comparator drugs (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The relative risk of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15% to 38%; P<0.0001). The relative risk of myocardial infarction was 2% higher for β- blockers than for the comparator drugs (RR, 1.02; 95% CI, 0.93 to 1.12), which was not statistically significant. The relative risk of all-cause mortality was 3% higher for β-blockers than for the comparator drugs (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
isradipine, lacidipine, lisinopril, losartan, verapamil), placebo				
Freemantle et al.[127] (1999) β-blockers (acebutolol, alprenolol, atenolol, betaxolol, carvedilol, labetalol, oxprenolol, pindolol, practolol, propranolol, sotalol, timolol and xamoterol) vs control (agents were not specified)	MA Patients with acute or past myocardial infarction	N=54,234 (82 trials) 6-48 months	Primary: All-cause mortality Secondary: Nonfatal reinfarction and withdrawal from treatment	Primary: The pooled random effects in short term trials demonstrated a mortality rate of 10.5% (3,062 out of 29,260 patients) which is a 4% reduction compared to the controlled groups (OR, 0.96; 95% CI, 0.85 to 1.08). The pooled random effects in long term trials demonstrated a mortality rate of 9.7% (2415 out of 24974 patients) which is 23% reduction when compared to the controlled groups (OR, 0.77;95% CI, 0.69 to 0.85). Individually, only four drugs achieved a statistically significant reduction in the death: propranolol (OR, 0.71; CI, 0.59 to 0.85]), timolol (OR, 0.59; CI, 0.46 to 0.77), metoprolol (OR, 0.80; CI, 0.66 to 0.96; and acebutolol (OR, 0.49; CI, 0.25 to 0.93). Secondary: A reduction in nonfatal re-infarctions of 0.9 events in every 100 (0.3 to 1.6) annually is suggested by this analysis; therefore about 107 patients would require treatment for 1 year to avoid one nonfatal reinfarction. Overall, 5,151 of 21,954 patients (23.5%) withdrew from treatment. with withdrawal occurring more often in the β-blocker groups. When comparing to placebo, the difference in annualized rate of withdrawal was 1.16 in 100 patients treated (1.16; 95% CI, 0.56 to 1.76).

*Agent is not longer manufactured in the Unites States
Drug regimen abbreviations: BID=twice daily, COER=controlled onset extended-release, CR=controlled release, ER=extended release, QD=daily, TID=three times daily, XL=extended release
Study abbreviations: BE=blinded endpoint, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, RR=relative risk, RMSSD=root mean square of successive RR intervals, SDNN=standard deviation of the normal RR intervals, SEM=standard error of the mean, SB=single-blinded, XO=cross-over
Miscellaneous abbreviations: ACE=angiotensin converting enzyme, AIx=augmentation index, aPWV=aortic pulse wave velocity, ARB=angiotensin receptor blocker, β-blockers=β-adrenergic blocking agents, bpm=beats per minute, CABG=coronary artery bypass graft, CCBs=calcium-channel blocking agents, CHD=coronary heart disease, CHF=congestive/chronic heart failure, DBP=diastolic blood pressure, ET=essential tremor, HCTZ=hydrochlorothiazide, HbA_{1c}=hemoglobin, LV=left ventricular, LVEF=left ventricular ejection fraction, NIDDM=noninsulin dependent diabetes mellitus, NYHA=New York Heart Association, pro-BNP= pro-B-type natriuretic peptide, QOL=quality of life, RAS=renin-angiotensin system, SBP=systolic blood pressure, TI=triangular index, WHO=World Health Organization

Additional Evidence

Dose Simplification
Nissinen et al. evaluated newly diagnosed hypertensive patients who received atenolol 100 mg and chlorthalidone 25 mg given as single entity products or as a fixed-dose combination.[38] Each of the active drug combinations significantly lowered standing, supine and postexercise blood pressure. There was no significant difference among the treatment regimens.

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 18. Relative Cost of the Beta-Adrenergic Blocking Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Acebutolol	capsule	Sectral®*	$$$	$
Atenolol	tablet	Tenormin®*	$$$-$$$$	$
Atenolol and chlorthalidone	tablet	Tenoretic®*	$$$	$
Betaxolol	tablet	Kerlone®*	$$-$$$	$$
Bisoprolol	tablet	Zebeta®*	$$$-$$$$	$-$$
Bisoprolol and hydrochlorothiazide	tablet	Ziac®*	$$$	$
Carvedilol	extended-release capsule, tablet	Coreg®*, Coreg CR®	$$$-$$$$	$
Labetalol	injection, tablet	Trandate®*	$$-$$$$	$
Metoprolol	extended-release tablet, injection, tablet	Lopressor®*, Toprol-XL®*	$$-$$$	$-$$$
Metoprolol and hydrochlorothiazide	tablet	Lopressor HCT®*	$$-$$$$	$$-$$$
Nadolol	tablet	Corgard®*	$$$-$$$$	$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Nadolol and bendroflumethiazide	tablet	Corzide®*	$$$-$$$$	$$$
Nebivolol	tablet	Bystolic®	$$$	N/A
Penbutolol	tablet	Levatol®	$$$	N/A
Pindolol	tablet	N/A	N/A	$
Propranolol	extended-release capsule, injection, solution, tablet	Inderal LA®*, InnoPran XL®	$$$-$$$$	$-$$$
Propranolol and hydrochlorothiazide	tablet	N/A	N/A	$
Sotalol	injection, tablet	Betapace®*, Betapace AF®*	$$$$-$$$$$	$$$
Timolol	tablet	N/A	N/A	$

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

X. Conclusions

All of the beta-adrenergic blocking agents (β-blockers) are approved for the treatment of hypertension, with the exception of sotalol.[1-27] Some of the products are also approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, migraine prophylaxis, myocardial infarction and pheochromocytoma.[1-27] These agents differ with regards to their adrenergic-receptor blockade, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1-3] All of the agents are available in a generic formulation, with the exception of nebivolol and penbutolol.

Due to improvements in cardiovascular morbidity and mortality, guidelines recommend the use of a β-blocker in patients with the following conditions: acute coronary syndromes, angina, arrhythmias, coronary artery disease, heart failure, left ventricular dysfunction, and post-myocardial infarction.[43-53,63-64,67,140-142] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[54,58,62,55] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[56-57] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[56-57] The selection of an antihypertensive agent should be based on compelling indications for use.[54-58,60-62] β-blockers are recommended as one of several initial options for the prevention of migraine headaches (metoprolol and propranolol), as well as for the treatment of essential tremor (propranolol).[66,68,143-144]

Numerous clinical trials have shown that the β-blockers can effectively lower blood pressure when administered alone or in combination with other antihypertensive agents.[29,31-40,42,73-85,111] Comparative studies have demonstrated similar efficacy among the β-blockers.[74-75,77,80-82,84,111] Most patients will require more than one antihypertensive agent to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[56-57] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.[38] In patients with chronic stable angina, β-blockers improve exercise tolerance and reduce the frequency of attacks. Head-to-head trials have demonstrated similar efficacy among several of the β-blockers.[118-123] In patients with heart failure, β-blockers (bisoprolol, carvedilol and metoprolol succinate) have been shown to reduce mortality, sudden death, cardiovascular deaths, and death due to heart failure.[94-97,107] Clinical trials supporting the use of carvedilol in patients with mild-to-severe heart failure were conducted with the immediate-release formulation. Data to support the use of the extended-release capsules for the treatment of heart failure is based on pharmacokinetic and pharmacodynamic parameters that demonstrated bioequivalence with the immediate-release formulation.[14]

In general, adverse events are similar among the β-blockers. Common adverse effects include fatigue, cold hands, dizziness and weakness. β-blockers that are more selective for the β_1-receptors (atenolol and metoprolol) may be safer to use in those with reactive airway disease as they are less likely to cause bronchospasm.[2]

There is insufficient evidence to support that one brand beta-adrenergic blocking agent 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 beta-adrenergic blocking 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 beta-adrenergic blocking 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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I. Overview

The movement of calcium ions is essential for the function of all types of muscle, including cardiac and vascular smooth muscle. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-3,17] Relaxation of coronary vascular smooth muscle increases the flow of oxygenated blood into the myocardium, while relaxation of arteriolar smooth muscle decreases peripheral vascular resistance.[18-20] Both coronary and systemic vasodilation serve to reduce cardiac workload.[22] The calcium-channel blocking agents include dihydropyridines and nondihydropyridines. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The nondihydropyridines also block the T-type calcium channel in the atrioventricular node.

The dihydropyridines are approved for the treatment of angina and hypertension.[1-16] Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease.[4] They are potent vasodilators and have little effect on cardiac muscle contractility or conduction. The dihydropyridines are available in a variety of single entity formulations. Amlodipine is also available in combination with benazepril, olmesartan, valsartan, or valsartan/hydrochlorothiazide. ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator.[1-3] Angiotensin II receptor antagonists block the angiotensin II receptor subtype AT_1, preventing the negative effects of angiotensin II, regardless of its origin. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.

The dihydropyridines that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the single entity products are available in a generic formulation, as well as the amlodipine/benazepril fixed-dose combination. This class was last reviewed in September 2008.

Table 1. Dihydropyridines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amlodipine	tablet	Norvasc®*	amlodipine
Amlodipine and benazepril	capsule	Lotrel®*	amlodipine and benazepril
Amlodipine and olmesartan	tablet	Azor®	none
Amlodipine and valsartan	tablet	Exforge®	none
Amlodipine, valsartan, and hydrochlorothiazide	tablet	Exforge HCT®	none
Clevidipine	injection^	Cleviprex®	none
Felodipine	extended-release tablet	N/A	felodipine
Isradipine	capsule*, extended-release tablet	DynaCirc CR®	isradipine
Nicardipine	capsule, injection, sustained-release capsule	Cardene IV®*, Cardene SR®	nicardipine
Nifedipine	capsule, extended-release tablet	Adalat CC®*, Procardia®*, Procardia XL®*	nifedipine
Nimodipine	capsule	Nimotop®*	nimodipine
Nisoldipine	extended-release tablet*	Sular®	nisoldipine

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
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 dihydropyridines are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of acute myocardial infarction, angina pectoris, heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Dihydropyridines

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation**[40] **(2003)**	Prophylactic Therapies in the Acute Phase • There is no case for using calcium-channel blocking agents for prophylactic purposes in the acute phase of an MI. Secondary Prevention • Dihydropyridines should only be prescribed for clear clinical indications, such as hypertension or angina.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI)**[38] **(2007)**	• No specific recommendation is made concerning the dihydropyridines.
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction**[39] **(2007)**	Secondary Prevention • Calcium-channel blocking agents should not routinely be used to reduce cardiovascular risk after an MI. • For patients who are stable after an MI, calcium-channel blockers may be used to treat hypertension and/or angina. • For patients with heart failure, amlodipine should be used, and verapamil, diltiazem and short-acting dihydropyridine agents should be avoided.
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**[23] **(2007)**	• Long-acting calcium-channel blocking agents (CCBs) or long-acting nitrates may be used if β-adrenergic blocking agents (β-blockers) are contraindicated. • Immediate-release and short-acting dihydropyridine CCBs can increase adverse cardiac events and should not be used. • Long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris**[22] **(2006)**	Therapy to Improve Prognosis • CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction (MI) and who do not have heart failure. Symptomatic Treatment and Treatment of Ischemia • If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB. Treatment of Syndrome X • Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination. Treatment of Vasospastic/Variant Angina • Treatment with CCBs is recommended. Nitrates may also be used if needed.

Clinical Guideline	Recommendation(s)
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease[26] (2004)**	Symptomatic Patients • The following agents are recommended to reduce symptoms only: NTG (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[24] (2007)**	Early Hospital Care • Immediate-release dihydropyridine calcium-channel blockers in the presence of adequate beta blockade may be considered in patients with ongoing ischemic symptoms or hypertension. • Immediate-release dihydropyridine calcium-channel blockers should not be administered to patients with UA/NSTEMI in the absence of a β-blocker. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge • Calcium-channel blockers are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. Variant (Prinzmetal's) Angina • Treatment with nitrates and CCBs is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions. Cardiovascular "Syndrome X" • Nitrates, β-blockers, and calcium-channel blockers (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)[25] (2007)**	Acute Treatment • CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline[28] (2010)**	Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • CCBs should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. Patients With Heart Failure and Coronary Artery Disease (CAD) • CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. Patients With Heart Failure and Hypertension • The use of an ACE inhibitor is recommended. • The addition of a β-blocker is recommended even if blood pressure is controlled. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine CCB (e.g., amlodipine or felodipine) or other antihypertensive drugs. Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended.

Clinical Guideline	Recommendation(s)
	• If blood pressure remains >130/80 mm Hg, a dihydropyridine CCB (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**[27] **(2009)**	Patients With Current or Prior Symptoms of Heart Failure (Stage C) • CCBs are not recommended as routine treatment for heart failure. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-blockers, angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[29] **(2008)**	• No specific recommendation is made concerning the dihydropyridines.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management**[34] **(2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • Several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an ARB or a CCB, and in recent large-scale trials for the ACE inhibitor/CCB combination. The ARB/CCB combination also appears to be rational and effective. These combinations can be recommended for priority use. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
European Society of Hypertension (ESH)/European	• The main benefits of antihypertensive therapy are due to lowering of blood pressure.

Clinical Guideline	Recommendation(s)
Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[32] (2007)**	• Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[33] (2006)**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • Initial therapy in patients younger than 55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[30] (2004)**	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes.

Clinical Guideline	Recommendation(s)
	• When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting CCBs may also be used. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2 to 4 times higher in African American patients. • CCBs may be useful in Raynaud's syndrome and certain arrhythmias. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[37] (2004)**	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB.

Clinical Guideline	Recommendation(s)
	• Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension**[31] **(2003)**	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[36] **(2003)**	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[35] **(2010)**	• Multiple drug therapy is generally required to achieve blood pressure goals. • No specific recommendation is made concerning the dihydropyridines.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the dihydropyridines 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 Dihydropyridines[1-16]

Indication	Amlodipine	Amlodipine/ Benazepril	Amlodipine/ Olmesartan	Amlodipine/ Valsartan	Amlodipine/ Valsartan/ HCTZ	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Angina Pectoris											
Treatment of chronic stable angina	✔ **							✔ **†			
Treatment of chronic stable angina in patients who remain symptomatic despite adequate doses of β-blockers and/or organic nitrates or who cannot tolerate those agents									✔ †§		
Treatment of vasospastic angina	✔ **								✔ †§		
Coronary Artery Disease (CAD)											
Reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%	✔										
Hypertension											
Treatment of hypertension	✔ *	✔ ‡	✔ *	✔	✔ ‡	✔ *	✔ *	✔ *	✔ *‖		✔ *
Miscellaneous											
For the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V)										✔	

*Alone or in combination with other antihypertensive agents.
**Alone or in combination with other antianginal agents.
‡This fixed dose combination drug is not indicated for initial therapy of hypertension.
†Immediate-release formulation.
§Extended-release formulation (excluding Adalat CC®).
‖Excludes Procardia®

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Dihydropyridines[1-16]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amlodipine	64-90	93	Liver, extensive	Renal (60) Feces (20-25)	30-50
Amlodipine and benazepril	A: 64-90 B: ≥37	A: 93 B: 96	A: Liver, extensive B: Liver, extensive	A: Renal (60) B: Renal (20) Feces (11-12)	A: 48 B: 10-11
Amlodipine and olmesartan	A: 64-90 O: 26	A: 93 O: 99	A: Liver, extensive O: Intestinal wall (100)	A: Renal (60) O: Renal (35-50) Feces (50-65)	A: 45 O: 7
Amlodipine and valsartan	A: 64-90 V: 25	A: 93 V: 95	A: Liver, extensive	A: Renal (60) V: Renal (13) Feces (83)	A: 30-50 V: 6
Amlodipine, valsartan, and hydrochlorothiazide	A: 64-90 V: 25 H: 50-75	A: 93 V: 95 H: 40-68	A: Liver, extensive V: Liver, minimal H: Not metabolized	A: Renal (60) V: Renal (7-13) Feces (83) H: Renal (>95)	A: 45 V: 6-9 H: 6-15
Felodipine	20	>99	Liver	Renal (70) Feces (10)	11-16
Isradipine	15-24	95	Liver	Renal (60-65) Feces (25-30)	8
Nicardipine	35	>95	Liver	Renal (60) Feces (35)	8-12
Nifedipine	IR: 40-77 ER: 65-89	92-98	Liver, extensive	Renal (80) Feces (20-40)	2
Nimodipine	13	>95	Liver, extensive	Renal (50) Feces (32)	1-2
Nisoldipine	5	>99	Liver, extensive	Renal (60-80)	7-12

A=amlodipine, B=benazepril, ER=extended-release, H=hydrochlorothiazide, IR=immediate-release, V=valsartan

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Dihydropyridines[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Angiotensin II receptor blockers (olmesartan, valsartan)	1	Potassium-sparing diuretics	The risk of hyperkalemia may be increased when potassium-sparing diuretics are co-administered with ACE inhibitors or ARBs.
Benazepril	1	Aldosterone blockers	Serious hyperkalemia, possibly with cardiac arrhythmias or arrest, may occur with the combination of aldosterone blockers and benazepril.
Benazepril	1	Potassium-sparing diuretics	The risk of hyperkalemia may be increased when potassium-sparing diuretics are co-administered with ACE inhibitors or ARBs.

Generic Name(s)	Significance Level	Interaction	Mechanism
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Hydrochlorothiazide	1	Lithium	Thiazide diuretics may promote enhanced proximal tubular reabsorption of lithium leading to elevated serum concentrations. Thiazide diuretics may increase the therapeutic and toxic effects of lithium.
Angiotensin II receptor blockers (olmesartan, valsartan)	2	ACE Inhibitors	Coadministration of ARBs and ACE inhibitors may be associated with an increased risk of renal dysfunction and/or hyperkalemia.
Angiotensin II receptor blockers (olmesartan, valsartan)	2	Lithium	Elevations in plasma lithium levels may occur.
Angiotensin II receptor blockers (olmesartan, valsartan)	2	Potassium preparations	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of olmesartan and potassium preparations.
Benazepril	2	Aliskiren	The risk of hyperkalemia may be increased when aliskiren is coadministered with benazepril.
Benazepril	2	Everolimus	The risk of angioedema may be increased with concurrent administration of everolimus and benazepril.
Benazepril	2	HIV protease inhibitors	Pharmacologic effects of benazepril may be increased by HIV protease inhibitors.
Benazepril	2	Imidazoles	Imidazoles may increase the plasma concentrations and pharmacologic effects of benazepril.
Benazepril	2	NSAIDs	The antihypertensive effects of benazepril may be decreased by NSAIDs. Nephrotoxicity associated with benazepril or NSAIDs may be increased by this drug combination.
Benazepril	2	Lithium	Pharmacologic effects of lithium may be increased by benazepril. Elevated lithium serum concentrations with toxicity may occur.
Benazepril	2	Potassium preparations	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of benazepril and potassium preparations.
Benazepril	2	Trimethoprim	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of trimethoprim and benazepril.
Benazepril	2	Vasopressin	Plasma concentrations of

Generic Name(s)	Significance Level	Interaction	Mechanism
		receptor antagonists	benazepril may be increased by co-administration of vasopressin receptor antagonists.
Dihydropyridines (amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine)	2	Azole antifungals	Dihydropyridine serum levels may increase resulting from a decrease metabolism due to CYP3A4 inhibition by azole antifungal agents.
Dihydropyridines (felodipine, nifedipine)	2	Erythromycin	Felodipine/nifedipine serum levels may increase due to inhibition of CYP3A by erythromycin.
Dihydropyridines (amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine)	2	HIV protease inhibitors	Dihydropyridine serum levels may increase resulting from a decrease metabolism due to CYP3A4 inhibition by protease inhibitors.
Dihydropyridines (nifedipine, nisoldipine)	2	Hydantoins	Dihydropyridine serum levels may decrease due to increased first-pass metabolism of nifedipine or nisoldipine caused by hydantoins.
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided.
Hydrochlorothiazide	2	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.
Nicardipine	2	Cyclosporine	Cyclosporine serum levels may increase due to inhibited metabolism by nicardipine.
Nifedipine	2	Carbamazepine	Carbamazepine may decrease plasma concentrations and effects of nifedipine.
Nifedipine	2	Cimetidine	The pharmacologic effects of nifedipine may be increased by cimetidine. The mechanism of this interaction is unknown.
Nifedipine	2	Quinidine	Plasma concentrations and pharmacologic effects of quinidine may be decreased by nifedipine. Plasma concentrations and pharmacologic effects of nifedipine may be increased by quinidine.
Nifedipine	2	Rifamycins	Nifedipine effects may be decreased due induced metabolism of nifedipine by CYP3A4, which is induced by rifamycins.
Nifedipine	2	Tacrolimus	Tacrolimus serum levels may be elevated due to inhibition of metabolism by nifedipine.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the dihydropyridines are listed in Tables 6 – 7. The boxed warnings for the dihydropyridines are listed in Tables 8 – 12.

Table 6. Adverse Drug Events (%) Reported with the Dihydropyridines (Amlodipine Products)[1-16]

Adverse Events	Amlodipine	Amlodipine/ Benazepril	Amlodipine/ Olmesartan	Amlodipine/ Valsartan	Amlodipine/ Valsartan/ HCTZ
Cardiovascular					
Arrhythmia	-	-	-	✔	-
Atrial fibrillation	-	-	-	1	-
Bradycardia	-	-	-	1	-
Cardiac murmur	-	-	-	✔	-
Chest pain	-	-	-	1	-
Edema	2-11	2	2-15	✔	7
Hypotension	-	-	✔	✔	-
Orthostatic hypotension	-	-	✔	1	-
Palpitations	1-5	✔	1-5	✔	-
Peripheral ischemia	1	-	-	1	-
Peripheral edema	18-26	✔	18-26	5-8	-
Pitting edema	-	-	-	✔	-
Postural hypotension	-	-	-	1	-
Pulse irregularity	-	-	-	✔	-
Tachycardia	-	-	-	✔	✔
Vasculitis	1	-	-	1	-
Ventricular tachycardia	1	-	-	1	-
Central Nervous System					
Abnormal dreams	1	-	-	1	-
Agitation	1	-	-	✔	-
Amnesia	1	-	-	✔	-
Anxiety	-	-	-	3	-
Apathy	1	-	-	✔	-
Asthenia	-	-	✔	✔	-
Ataxia	-	-	-	✔	-
Carpal tunnel syndrome	-	-	-	✔	-
Cervicobrachial syndrome	-	-	-	✔	-
Depersonalization	1	-	-	1	-
Depression	-	-	-	✔	-
Dizziness	1	1	1-3	2	8
Headache	7	2	-	11	5
Hypoesthesia	-	-	-	✔	-
Insomnia	-	-	-	✔	-
Migraine	-	-	-	✔	-
Nervousness	1	✔	-	1	-
Paresthesia	-	-	-	✔	-
Peripheral neuropathy	1	-	-	1	-
Postural dizziness	-	✔	-	1	<1
Pyrexia	-	-	-	✔	-
Sciatica	-	-	-	✔	-
Sinus headache	-	-	-	✔	-
Somnolence	<2	✔	<2	3	✔
Syncope	-	✔	-	1	✔
Tremor	-	-	-	1	✔
Vertigo	1	-	-	✔	-
Dermatologic					

Adverse Events	Amlodipine	Amlodipine/ Benazepril	Amlodipine/ Olmesartan	Amlodipine/ Valsartan	Amlodipine/ Valsartan/ HCTZ
Alopecia	-	-	✔	✔	-
Cold and clammy skin	1	-	-	✔	-
Dermatitis	-	-	-	✔	-
Eczema	-	-	-	✔	-
Erythema	-	-	-	✔	-
Erythema multiforme	1	-	-	1	-
Exanthema	-	-	-	✔	-
Flushing	1-3	✔	1-5	✔	-
Hyperhidrosis	-	-	-	✔	-
Pruritus	1	-	✔	✔	✔
Rash	-	✔	✔	✔	✔
Rash, erythematous	-	-	-	1	-
Rash, maculopapular	-	-	-	1	-
Skin discoloration	1	-	-	✔	-
Skin dryness	1	-	-	✔	-
Urticaria	1	-	✔	✔	-
Endocrine and Metabolic					
Gout	-	-	-	✔	-
Gynecomastia	✔	-	✔	-	-
Diabetes mellitus	-	-	-	✔	-
Thirst	1	-	-	1	-
Gastrointestinal					
Abdominal discomfort	-	-	-	✔	-
Abdominal distension	-	-	-	✔	-
Abdominal pain	2	✔	-	3	-
Anorexia	1	-	-	1	-
Colitis	-	-	-	✔	-
Constipation	1	✔	-	✔	✔
Diarrhea	-	✔	-	3	✔
Dry mouth	-	✔	-	✔	✔
Dyspepsia	-	-	-	✔	2
Dysphagia	1	-	-	1	-
Flatulence	1	-	-	✔	-
Gastritis	-	-	-	✔	✔
Gastroenteritis	-	-	-	✔	-
Hemorrhoids	-	-	-	✔	✔
Increased appetite	-	-	-	✔	-
Jaundice	✔	-	✔	-	-
Loose stools	1	-	-	✔	-
Nausea	3	✔	-	3	2
Pancreatitis	1	-	-	1	-
Vomiting	-	-	✔	✔	-
Genitourinary					
Cystitis	-	-	-	✔	-
Dysuria	-	-	-	✔	-
Erectile dysfunction	-	-	-	✔	✔
Hematuria	-	-	-	✔	-
Impotence	-	✔	-	✔	-
Micturition disorder	1	-	-	1	-
Nephrolithiasis	-	-	-	✔	-
Nocturia	1	-	✔	1	-
Pollakiuria	-	-	-	✔	-
Polyuria	-	✔	-	✔	-

Adverse Events	Amlodipine	Amlodipine/ Benazepril	Amlodipine/ Olmesartan	Amlodipine/ Valsartan	Amlodipine/ Valsartan/ HCTZ
Sexual dysfunction	1	-	-	1	-
Urinary frequency	1	-	✔	✔	-
Urinary tract infection	-	-	-	✔	-
Hematological					
Leukopenia	-	-	-	1	-
Purpura	1	-	-	1	-
Thrombocytopenia	1	-	-	1	-
Laboratory Test Abnormalities					
Blood urea nitrogen increased	-	-	-	5-17	-
Creatinine increases	-	-	-	✔	-
Hepatic enzyme elevations	✔	-	✔	✔	-
Hypercholesterolemia	-	-	-	✔	-
Hyperglycemia	1	-	-	1	-
Hyperkalemia	-	✔	-	3-10	-
Musculoskeletal					
Arthralgia	-	-	-	✔	✔
Arthrosis	1	-	-	1	-
Back pain	1	✔	-	✔	2
Hypertonia	-	-	-	✔	-
Joint sprain	-	-	-	✔	-
Joint swelling	-	-	-	✔	✔
Limb injury	-	-	-	✔	-
Malaise	1	-	-	1	-
Muscle cramps	1	✔	-	1	-
Muscle spasms	-	-	-	✔	2
Muscle weakness	-	-	-	✔	✔
Musculoskeletal chest pain	-	-	-	✔	-
Myalgia	1	✔	-	✔	-
Osteoarthritis	-	-	-	✔	✔
Pain	1	-	-	✔	-
Rhabdomyolysis	✔	-	✔	-	-
Twitching	1	-	-	✔	-
Respiratory					
Bronchitis	-	-	-	✔	-
Cough	-	3	-	2	✔
Dysphonia	-	-	-	✔	-
Dyspnea	-	-	-	1	-
Epistaxis	1	-	-	✔	-
Influenza	-	-	-	2	-
Nasal congestion	-	-	-	✔	✔
Nasopharyngitis	-	-	-	4	2
Pharyngitis	-	✔	-	✔	-
Pharyngolaryngeal pain	-	-	-	✔	✔
Pharyngotonsillitis	-	-	-	✔	-
Pneumonia	-	-	-	✔	-
Rhinitis	-	-	-	✔	-
Seasonal allergies	-	-	-	✔	-
Sinus congestion	-	-	-	✔	-
Sinusitis	-	-	-	✔	-
Upper respiratory tract infection	-	-	-	3	-
Special Senses					
Abnormal visual accommodation	-	-	-	✔	-
Conjunctivitis	1	-	-	1	-

Adverse Events	Amlodipine	Amlodipine/ Benazepril	Amlodipine/ Olmesartan	Amlodipine/ Valsartan	Amlodipine/ Valsartan/ HCTZ
Diplopia	1	-	-	1	-
Eye pain	1	-	-	1	-
Ear pain	-	-	-	✔	-
Parosmia	1	-	-	✔	-
Taste perversion	-	-	-	✔	-
Tinnitus	1	-	-	✔	-
Visual disturbance	-	-	-	✔	-
Xerophthalmia	1	-	-	✔	-
Other					
Acute renal failure	-	-	✔	✔	-
Allergic reaction	1	-	✔	1	-
Angioedema	1	-	✔	1	-
Contusion	-	-	-	✔	-
Epicondylitis	-	-	-	✔	-
Fatigue	4.5	-	-	✔	2
Gingival hyperplasia	1	-	-	1	-
Hot flush	1	-	-	✔	-
Hypersensitivity	-	-	-	✔	-
Lymphadenopathy	-	-	-	✔	-
Rigors	1	-	-	1	-
Tooth abscess	-	-	-	✔	-
Toothache	-	-	-	✔	-
Tonsillitis	-	-	-	✔	-
Viral infection	-	-	-	✔	-
Weight gain	1	-	-	1	-
Weight loss	1	-	-	1	-

✔ Percent not specified
- Event not reported

Table 7. Adverse Drug Events (%) Reported with the Dihydropyridines (Drugs F - N)[1-16]

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Cardiovascular						
Angina (increased)	-	-	6	-	-	2
Arrhythmia	1-2	-	-	-	-	-
Atrial fibrillation	-	≤1	<1	-	-	-
Bradycardia	-	-	-	-	≤1	-
Cardiac failure	-	≤1	-	-	-	-
Cerebrovascular accident	-	-	-	-	-	1
Chest pain	1-2	-	-	-	-	-
Edema	-	4-36	≤1	-	≤1	-
Electrocardiogram abnormalities	-	-	≤1	-	≤1	-
Epistaxis	-	≤1	-	-	-	-
Erythromelalgia	-	-	-	1	-	-
Hypotension	1-2	≤1	-	5	1-50	-
Myocardial infarction	1-2	≤1	≤1	✔	-	-
Orthostatic hypotension	-	-	-	-	-	1
Palpitations	<3	1-5	3-4	<7	-	3
Pedal edema	-	-	6-8	-	-	-
Peripheral edema	2-17	-	✔	7-10	-	22
Pericarditis	-	-	1	-	-	-
Peripheral ischemia	-	-	✔	-	-	-

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Postural hypotension	-	-	≤1	-	-	-
Pulse irregularity	1-2	-	-	-	-	-
Rebound vasospasm	-	-	-	-	1	-
Tachycardia	1-2	1-3	1-4	-	≤1	-
Vasodilatation/vasodilation	-	-	1-5	-	-	4
Ventricular fibrillation	-	≤1	-	1	-	-
Ventricular tachycardia	-	-	≤1	-	-	-
Central Nervous System						
Anxiety	1-2	-	✔	-	-	-
Asthenia	2-4	1-6	-	<3	-	-
Ataxia	-	-	-	1	-	-
Balance difficulties	-	-	-	<2	-	-
Chills	-	-	-	<2	-	1
Confusion	-	-	✔	-	-	-
Depression	1-2	≤1	✔	1	≤1	-
Dizziness	3-4	3-8	1-7	4-27	-	5
Drowsiness	-	≤1	-	-	-	-
Fatigue	-	3-9	-	6	-	-
Headache	11-15	10-22	6-15	10-23	≤1	22
Insomnia	1-2	≤1	≤1	<3	-	-
Irritability	1-2	-	-	-	-	-
Migraine	-	-	-	1	-	1
Nervousness	1-2	≤1	≤1	<7	-	-
Numbness	-	≤1	-	-	-	-
Paresthesia	1-2	≤1	≤1	<3	-	-
Sleep disturbance	-	-	-	<2	-	-
Somnolence	1-2	-	≤1	<3	-	-
Stroke	-	≤1	-	-	-	-
Syncope	1-2	≤1	≤1	-	-	-
Transient ischemic attack	-	≤1	-	-	-	-
Tremor	-	-	≤1	<8	-	-
Vertigo	-	-	✔	1	-	-
Dermatologic						
Acne	-	-	-	-	≤1	-
Alopecia	-	-	-	<1	-	-
Dermatitis	-	-	-	1-2	-	-
Erythema	1-2	-	-	-	-	-
Flushing	4-7	1-5	6-10	3-25	-	-
Hematoma	-	-	-	-	1	-
Hyperhidrosis	-	≤1	11	<2	-	-
Pruritus	-	≤1	-	<2	1	-
Rash	<2	≤3	≤1	<3	1-2	2
Urticaria	1-2	≤1	-	<2	-	-
Endocrine and Metabolic						
Breast pain	-	-	-	1	-	-
Decreased libido	1-2	-	-	-	-	-
Gout	-	-	-	1	-	-
Gynecomastia	1-2	-	-	-	-	-
Gastrointestinal						
Abdominal discomfort	-	≤5	-	<2	-	-
Abdominal pain	1-2	<1	-	<3	-	-
Acid regurgitation	1-2	-	-	-	-	-
Anorexia	-	-	-	-	-	1
Colitis	-	-	-	-	-	1

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Constipation	<2	1-4	≤1	3	-	-
Diarrhea	1-2	≤3	-	<2	2-4	-
Dry mouth	1-2	≤1	≤1	<3	-	-
Dyspepsia	1-4	-	1-2	3-11	-	-
Dysphagia	-	-	-	-	-	1
Flatulence	1-2	-	-	<2	-	1
Gastritis	-	-	-	-	-	1
Gastrointestinal hemorrhage	-	-	-	-	1	1
Gastrointestinal symptoms	-	-	-	-	≤2	-
Hepatitis	-	-	-	-	1	1
Increased appetite	-	≤1	-	-	-	1
Jaundice	-	-	-	-	1	-
Nausea	1-2	1-5	2-5	3-11	≤1	2
Vomiting	1-2	≤1	≤5	-	-	-
Genitourinary						
Decreased libido	-	≤1	-	-	-	-
Dysuria	1-2	≤1	-	1	-	-
Hematuria	-	-	-	1	-	-
Impotence	1-2	≤1	✔	<3	-	-
Nocturia	-	≤1	-	1	-	-
Pollakiuria	-	1-3	-	-	-	-
Polyuria	1-2	-	-	1-3	-	-
Sexual dysfunction	-	-	-	<2	-	-
Urinary frequency/urgency	1-2	-	-	-	-	-
Hematological						
Anemia	1-2	-	-	<1	1	-
Leukopenia	-	≤1	-	-	-	-
Thrombocytopenia	-	-	✔	-	1	-
Laboratory Test Abnormalities						
Hepatic enzyme elevations	1-2	≤1	✔	-	≤1	-
Hyponatremia	-	-	-	-	1	-
Musculoskeletal						
Arthralgia	1-2	-	✔	<3	-	-
Back pain	1-2	≤1	-	1	-	-
Hypertonia	-	-	✔	1	-	-
Inflammation	-	-	-	<2	-	-
Joint sprain	1-2	≤1	-	-	-	-
Malaise	-	-	≤1	1	-	1
Muscle cramps	1-2	≤1	-	3-8	≤1	-
Muscle weakness	-	≤1	-	10-12	-	-
Musculoskeletal chest pain	1-2	2-3	-	<3	-	-
Myalgia	1-2	-	1	1	-	-
Neck pain	-	≤1	✔	-	-	-
Pain	-	-	≤1	<3	-	-
Stiffness	-	-	-	<2	-	-
Respiratory						
Bronchitis	1-2	-	-	-	-	-
Cough	1-2	≤1	-	1-6	-	-
Dyspnea	1-2	<3	≤1	3-6	≤1	-
Epistaxis	1-2	-	-	1	-	-
Influenza/flu-like illness	1-2	-	-	-	-	1
Nasal congestion	1-2	≤1	✔	2-6	-	-
Nasopharyngitis	1-2	-	-	-	-	-
Pharyngitis	-	-	-	-	-	5

Adverse Events	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Pharyngolaryngeal pain	-	≤1	-	-	-	-
Shortness of breath	-	≤1	-	<2	1	-
Sinusitis	1-2	-	✔	1	-	3
Sore throat	-	-	✔	6	-	-
Upper respiratory tract infection	1-4	-	-	1	-	-
Special Senses						
Abnormal visual accommodation	-	-	✔	1	-	-
Blurred vision	-	-	✔	<2	-	-
Conjunctivitis	-	-	✔	-	-	-
Ear pain/disorder	-	-	✔	-	-	-
Taste perversion	-	-	-	1	-	-
Tinnitus	-	-	✔	<5	-	-
Visual disturbance	1-2	≤1	-	<5	-	-
Other						
Allergic reaction	-	-	✔	-	-	-
Angioedema	1-2	-	-	-	-	-
Cellulitis	-	-	-	-	-	1
Contusion	1-2	-	-	-	-	-
Facial edema	-	-	-	-	-	1
Fever	-	≤1	-	<2	-	1
Gingival hyperplasia	1-2	-	-	-	-	1
Glossitis	-	-	-	-	-	1
Hot flush	-	-	✔	-	-	-
Infection	-	-	✔	-	-	-
Rigors	-	-	-	1	-	-
Warm sensation	1-2	-	-	-	-	-
Weight gain	-	≤1	-	1	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Amlodipine/Benazepril[1]

WARNING
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue therapy as soon as possible.

Table 9. Boxed Warning for Amlodipine/Olmesartan[1]

WARNING
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue therapy as soon as possible.

Table 10. Boxed Warning for Amlodipine/Valsartan[1]

WARNING
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue therapy as soon as possible.

Table 11. Boxed Warning for Amlodipine/Valsartan/Hydrochlorothiazide[1]

WARNING
When pregnancy is detected, discontinue therapy as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury or death to the developing fetus.

Table 12. Boxed Warning for Nimodipine[1]

WARNING
Do not administer nimodipine intravenously (IV) or by other parenteral routes. Deaths and serious, life-threatening adverse reactions have occurred when the contents of nimodipine capsules have been injected parenterally.

VII. Dosing and Administration

The usual dosing regimens for the dihydropyridines are listed in Table 13.

Table 13. Usual Dosing Regimens for the Dihydropyridines[1-16]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amlodipine	Chronic Stable or Vasospastic Angina: 5 to 10 mg daily; maximum, 10 mg daily Coronary Artery Disease: 5 to 10 mg daily; maximum, 10 mg daily Hypertension: Initial, 5 mg daily; maintenance, 5 to 10 mg daily; maximum, 10 mg daily	Children 6 to 17 years of age: Hypertension: Initial: 2.5 mg daily; maintenance 2.5 to 5 mg daily; maximum 5 mg daily	Tablet: 2.5 mg 5 mg 10 mg
Amlodipine and benazepril	Hypertension: This fixed combination drug is not indicated for the initial therapy of hypertension. Initiate combination therapy after failure on monotherapy and titrate dose by clinical effect. The combination may be substituted for the titrated individual components.	Safety and efficacy in children have not been established.	Capsule: 2.5 mg-10 mg 5 mg-10 mg 5 mg-20 mg 5 mg-40 mg 10 mg-20 mg 10 mg-40 mg
Amlodipine and olmesartan	Hypertension: Initial: 5/20 mg once daily; maximum, 10/40 mg	Safety and efficacy in children have not been established.	Tablet: 5 mg-20 mg 5 mg-40 mg 10 mg-20 mg 10 mg-40 mg
Amlodipine and valsartan	Hypertension: Initial: 5/160 mg once daily; maximum, 10/320 mg	Safety and efficacy in children have not been established.	Tablet: 5 mg-160 mg 5 mg-320 mg 10 mg-160 mg 10 mg-320 mg
Amlodipine, valsartan, hydrochlorothiazide	Hypertension: This fixed combination drug is not indicated for the initial therapy of hypertension. This product is dosed once daily. The	Safety and efficacy in children have not been established.	Tablet: 5 mg-160 mg-12.5 mg 5 mg-160 mg-25 mg 10 mg-160 mg-12.5 mg 10 mg-160 mg-25 mg 10 mg-320 mg-25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum recommended dose is 10/320/25 mg.		
Felodipine	Hypertension: Initial: 5 mg daily; maintenance 2.5 to 10 mg daily	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg
Isradipine	Hypertension: IR: initial, 2.5 mg twice daily; maximum, 20 mg daily ER: initial, 5 mg daily; maximum, 20 mg daily	Safety and efficacy in children have not been established.	Capsule (IR): 2.5 mg 5 mg Tablet (ER): 5 mg 10 mg
Nicardipine	Chronic Stable Angina Capsule IR: initial, 20 mg three times daily; maintenance, 20 to 40 mg three times daily Hypertension: Capsule IR: initial, 20 mg three times daily; maintenance, 20 to 40 mg three times daily Capsule ER: initial, 30 mg twice daily; maintenance, 30 to 60 mg twice daily	Safety and efficacy in children have not been established.	Capsule (IR): 20 mg 30 mg Capsule (ER): 30 mg 45 mg 60 mg Injection: 20 mg/200 ml 40 mg/200 ml 25 mg/10 ml
Nifedipine	Chronic Stable Angina Capsule IR: initial, 10 mg three times daily; maintenance, 10 to 20 mg three times daily; maximum, 180 mg daily Tablet ER: initial, 30 or 60 mg daily; maintenance, 30 to 90 mg; maximum, 120 mg daily Hypertension Tablet ER: initial, 30 or 60 mg daily; maintenance, 30 to 90 mg; maximum, 120 mg daily Vasospastic Angina Capsule IR: initial, 10 mg three times daily; maintenance, 20 to 30 mg three to four times daily; maximum, 180 mg daily Tablet ER: initial, 30 or 60 mg daily; maintenance, 30 to 90 mg; maximum, 120	Safety and efficacy in children have not been established.	Capsule (IR): 10 mg 20 mg Tablet (ER): 30 mg 60 mg 90 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg daily		
Nimodipine	Subarachnoid Hemorrhage 60 mg every 4 hours for 21 consecutive days	Safety and efficacy in children have not been established.	Capsule: 30 mg
Nisoldipine	Hypertension Tablet (Sular®): initial, 17 mg once daily; maintenance, 17 to 34 mg daily; maximum, 34 mg daily Tablet (generic): initial, 20 mg once daily; maintenance, 20 to 40 mg daily; maximum, 60 mg daily	Safety and efficacy in children have not been established.	Tablet (ER): 8.5 mg 17 mg 20 mg 25.5 mg 30 mg 34 mg 40 mg

ER=extended-release, IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the dihydropyridines are summarized in Table 14.

Table 14. Comparative Clinical Trials with the Dihydropyridines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Angina				
Koenig et al.[41] (1997) Amlodipine 5 to 10 mg QD for 4 weeks vs felodipine ER 5 to 10 mg QD for 4 weeks	DB, PRO, RCT, XO Patients, age 30 to 80 years, who have a history of angina, a positive exercise-stress test or positive 24-hour ambulatory monitoring, and ≥6 ischemic episodes in 24 hours	N=52 8 weeks	Primary: Number of ST-segment depressions in 24 hours of ambulatory monitoring Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression, length of ischemic episode, adverse events	Primary: Significant reductions from baseline were seen in both groups for the number of ST-segment depressions, from 19.9 at baseline for both groups to 2.3 for amlodipine and 2.4 for felodipine (P<0.001 for both from baseline; P=0.83 between treatments). Secondary: Total and mean duration of each ST-segment depression episode, maximum ST depression and length of ischemic episode were significantly different from baseline for both treatment groups but treatments were not significantly different (P<0.001 for all from baseline, P=0.53, P=0.40, P=0.68, P=0.35, respectively between treatments). Adverse event rates similar between the treatments.
Cardiovascular Outcomes Trials				
Pitt et al.[60] (2000) PREVENT Amlodipine 5 to 10 mg QD vs placebo	DB, MC, PC, RCT Men and women, age 30 to 80 years with angiographic evidence of coronary artery disease, DBP <95 mm Hg, total cholesterol 325 mg/dL, fasting blood glucose <200	N=825 3 years	Primary: Change in mean minimal diameter with a quantitative coronary angiography Secondary: Progression of atherosclerosis in the carotid arteries assessed by B-	Primary: Change, reduction, in the minimal diameter was similar between the amlodipine group and the placebo group (0.084 vs 0.0095 P=0.38). Secondary: Amlodipine treatment significantly decreased the progression of atherosclerosis as compared to placebo treatment, a 0.013 mm decrease for the amlodipine group vs a 0.033 mm increase with placebo (P=0.007). There was no difference in all-cause mortality between amlodipine and placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	mg/dL		mode ultrasonography for intimal-medial thicknesses, all-cause mortality, occurrence of major fatal/nonfatal vascular events or procedures, adverse events	There was no difference in occurrence of fatal and nonfatal vascular events between the treatment groups (HR, 0.82; 95% CI, 0.47 to 1.42). Amlodipine treatment significantly reduced the occurrence of hospitalized congestive heart failure and unstable angina (HR, 0.65; 95% CI, 0.47 to 0.91) and coronary revascularizations (HR, 0.57; 95% CI, 0.41 to 0.81) and combined overall procedures (HR, 0.69; 95% CI, 0.52 to 0.92). There was no significant difference between groups in rates of adverse events: cancer rate (HR, 2.13; 95% CI, 0.90 to 5.21) and bleeding episode (HR, 1.42; 95% CI, 0.88 to 2.30).
Dahlöf et al.[66] (2005) ASCOT-BPLA Amlodipine 5 to 10 mg QD (with option to add perindopril 4 to 8 mg QD as required) vs atenolol 50 to 100 mg QD (with option of adding bendro-flumethiazide 1.25 to 2.5 mg QD as required)	DB, MC, RCT Patients, age 40 to 79 years of age, with hypertension and at least 3 other cardiovascular risk factors	N=19,257 5.5 years	Primary: Nonfatal myocardial infarction and fatal coronary heart disease Secondary: All-cause mortality, total stroke, primary endpoint minus silent myocardial infarction, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart impairment	Primary: There was no significant difference in rates of nonfatal myocardial infarction and fatal coronary heart disease between amlodipine treatment and atenolol treatment (8.2 events per 1,000 patient-years vs 9.1 events per 1,000 patient-years (HR, 9.1; 95% CI, 0.79 to 12). Secondary: The amlodipine group had significant reductions in the following endpoints as compared to the atenolol group: nonfatal myocardial infarction (excluding silent myocardial infarction) and fatal coronary heart disease (P=0.0458), total coronary events (P=0.0070), total cardiovascular events and procedures (P<0.0001), all-cause mortality (P=0.0247), cardiovascular mortality (P=0.001), fatal and nonfatal stroke (P=0.0003).
Nissen et al.[67] (2004) CAMELOT	DB, MC, PC, RCT Men and women, age 30 to 79 years	N=1,997 24 months	Primary: Incidence of adverse cardiovascular	Primary: Significantly fewer cardiovascular events occurred in the amlodipine group as compared to the placebo group (110 vs 151; HR, 0.69; 95% CI, 0.54 to 0.88; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 10 mg QD vs enalapril 20 mg QD vs placebo	old who required coronary angiography for evaluation for chest pain or percutaneous coronary intervention, with a DBP <100 mm Hg, who had 1 or more lesion with greater than 20% stenosis on angiograph		event (cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for congestive heart failure, stroke or transient ischemic attack, new diagnosis of peripheral vascular disease) Secondary: Incidence of adverse events and revascularization	Rates of cardiovascular events were similar between the amlodipine treatment group and the enalapril treatment group (110 vs 136; HR, 0.81; 95% CI, 0.63 to 14; P=0.10). Rates of cardiovascular events were similar between the enalapril treatment group and the placebo treatment group (136 vs 151; HR, 0.85; 95% CI, 0.67 to 17; P=0.16). Secondary: The incidence of adverse events was not significantly different among treatment groups (P values not significant). No difference was found among all groups for the endpoint of all-cause mortality (P values not significant). The incidence of revascularization was significantly lower in the amlodipine group (4.1%) as compared to the placebo group (7.9%) (P=0.002). No significant difference was seen for amlodipine compared to enalapril, or enalapril compared to placebo (P=0.09 and P=0.17).
ALLHAT Collaborative Research Group[69] (2002) ALLHAT Amlodipine 2.5 to 10 mg QD vs lisinopril 10 to 40 mg QD	AC, DB, MC, RCT Men and women, age 55 years old and older, with hypertension and at least 1 coronary heart disease risk factor	N=33,357 4.9 years (average follow-up)	Primary: Combined fatal coronary heart disease and nonfatal myocardial infarction Secondary: All-cause mortality, stroke, combined coronary heart disease, combined cardiovascular	Primary: No significant difference was observed between amlodipine and chlorthalidone in combined fatal coronary heart disease and nonfatal myocardial infarction (RR, 0.98; 95% CI, 0.90 to 17). No significant difference was observed between lisinopril and chlorthalidone in combined fatal coronary heart disease and nonfatal myocardial infarction (RR, 0.99; 95% CI, 0.91 to 18). Secondary: No significant difference was observed between amlodipine and chlorthalidone in all-cause mortality, combined coronary heart disease, stroke, combined cardiovascular disease, angina, coronary revascularization, and peripheral artery disease (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs chlorthalidone 12.5 to 25 mg QD			disease	The amlodipine group had a 38% greater risk of heart failure than chlorthalidone (P<0.001). No significant difference was observed between lisinopril and chlorthalidone in all-cause mortality, combined coronary heart disease and peripheral artery disease (P>0.05). The lisinopril group had a 15% greater risk of stroke than the chlorthalidone group (P=0.02), a 10% greater risk for combined cardiovascular disease (P<0.001), and an 11% greater risk for hospitalized/treated angina (P=0.01).
Black et al.[70] (2008) ALLHAT Amlodipine 2.5 to 10 mg QD vs lisinopril 10 to 40 mg QD vs chlorthalidone 12.5 to 25 mg QD	MC, RCT Men and women, age 55 years old and older, with hypertension and metabolic syndrome	N=17,515 4.9 years	Primary: Fatal coronary heart disease and nonfatal myocardial infarction Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease	Primary: For patients with metabolic syndrome, there was no significant difference in rates of coronary heart disease and nonfatal myocardial infarction with amlodipine vs chlorthalidone (RR, 0.96; 95% CI, 0.79 to 1.16), or lisinopril vs chlorthalidone (RR, 15; 95% CI, 0.88 to 1.27). Secondary: For patients with metabolic syndrome, there were no significant differences found between amlodipine vs chlorthalidone in all secondary endpoints (P value not significant). For patients without metabolic syndrome, amlodipine treatment was associated with significantly more heart failure, but in patients with metabolic syndrome, there was no difference (P=0.03). Patients with metabolic syndrome who received lisinopril experienced more heart failure and cardiovascular disease than those who received chlorthalidone (RR, 1.31; 95% CI, 14 to 1.64 and RR, 1.19; 95% CI, 17 to 1.32).
Ogihara et al.[54] (2008) CASE-J Amlodipine 2.5 to 10 mg QD	AC, MC, OL, RCT Patients with high risk hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg in patients <70	N=4,703 Up to 4 years	Primary: First fatal/nonfatal cardiovascular event (composite of sudden death, cerebrovascular events, cardiac	Primary: A total of 134 patients experienced a cardiovascular event in each treatment regimen (HR, 10; 95% CI, 0.78 to 1.27; P=0.969). Secondary: All-cause death rates did not differ between treatments, 73 deaths in the candesartan group and 86 in the amlodipine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs candesartan 4 to 12 mg QD	years old or SBP ≥160 mm Hg or DBP ≥90 mm Hg in patients ≥70 years old), with either type 2 diabetes, history of stroke or ischemic attack, left ventricular hypertrophy, proteinuria or serum creatinine ≥1.3 mg/dL		events including heart failure, angina pectoris, acute myocardial infarction, renal events, including serum creatinine increases, vascular events, including dissecting aortic aneurysm or arteriosclerotic occlusion Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events	New-onset diabetes occurred in significantly fewer patients in the candesartan group than the amlodipine group (HR, 0.64; 95% CI, 0.43 to 0.97; P=0.033). A total of 125 (5.4%) patients in the candesartan group and 134 (5.8%) of patients in the amlodipine group discontinued due to adverse events.
Julius et al.[106] (2004) VALUE Amlodipine 5 to 10 mg QD vs valsartan 80 to 160 mg QD	DB, PG, RCT Patients ≥50 years old with treated or untreated hypertension and history of CVD, stroke, or diabetes, previous medications were discontinued at trial onset	N=15,245 4.2 years (mean)	Primary: Time to first cardiac event (cardiac morbidity and mortality) Secondary: Fatal and nonfatal myocardial infarction, fatal and nonfatal heart failure and fatal and nonfatal stroke, all-cause mortality, new onset diabetes	Primary: There were no differences in the primary composite end point between the valsartan and amlodipine groups (10.6% vs 10.4%; P=0.49). Secondary: There was a higher incidence of myocardial infarction (4.8% vs 4.1%; P=0.02) in patients receiving valsartan than amlodipine. There was no difference in the incidence of heart failure (4.6% vs 5.3%; P=0.12), stroke (4.2% vs 3.7%; P=0.08), and all-cause mortality (11% vs 10.8%; P=0.45) between valsartan- and amlodipine-treated patients. New onset diabetes occurred less with valsartan (13.1%) vs amlodipine (16.4%; P<0.001). Combined target blood pressure (<140/90 mm Hg) was achieved in 58%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 62% of patients receiving valsartan and amlodipine, respectively.
Zanchetti et al.[64] (2006) VALUE Amlodipine 5 mg QD vs valsartan 80 mg QD	DB, PG, RCT (subgroup analysis of VALUE trial) Patients with hypertension	N=15,245 4.2 years	Primary: Time to first cardiac event, analyzed by subgroup Secondary: Myocardial infarction, heart failure and stroke	Primary: The only significant result of the analyses by subgroup for time to first cardiac event was sex; women in the valsartan group experienced more cardiac events as compared to men in the valsartan group (HR for women, 1.21; 95% CI, 13 to 1.42; HR for men, 0.94; 95% CI, 0.82 to 17; P=0.016). The VALUE trial showed no difference in the primary outcome as well as in cardiac morbidity and mortality between amlodipine treatment and valsartan treatment. SBP and DBP were lower, as was incidence of myocardial infarction, in the amlodipine treatment group as compared to the valsartan group. Secondary: Male patients treated with valsartan had a significantly lower incidence of heart failure than males treated with amlodipine (P<0.001 for male vs female difference; for men, HF rates with valsartan were 4.1% vs amlodipine 5.8% [HR, 0.73; 95% CI, 0.60 to 0.88]; for women, rates were valsartan 5.3% vs amlodipine 4.6%, [HR, 1.18; 95% CI, 0.95 to 1.47]). Patients without a history of stroke had a greater reduction in stroke risk if treated with amlodipine (valsartan 3.4% vs amlodipine 2.6%; HR, 1.34; 95% CI, 19 to 1.65).
Jamerson et al.[97] (2008) ACCOMPLISH Amlodipine 5 mg QD and benazepril 20 mg QD vs benazepril 20 mg QD and HCTZ	DB, AC, MC, RCT Adults with hypertension and at high risk of cardiovascular events	N=11,506 36 months	Primary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and	Primary: There were 552 primary-outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-hydrochlorothiazide group (11.8%), representing an absolute risk reduction with benazepril-amlodipine therapy of 2.2% and a relative risk reduction of 19.6% (HR, 0.80, 95% CI, 0.72 to 0.90; P<0.001). Secondary: There were 288 events (5%) in the benazepril-amlodipine group as compared with 364 (6.3%) in the benazepril-hydrochlorothiazide group, representing an absolute risk reduction of 1.3% and a relative risk reduction of 21.2% (hazard ratio, 0.79; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12.5 mg QD			coronary revascularization Secondary: Death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke	
Hansson et al.[71] (1999) STOP-Hypertension Felodipine 2.5 mg or isradipine 2.5 mg QD vs enalapril 10 mg or lisinopril 10 mg QD vs atenolol 50 mg or metoprolol 100 mg or pindolol 5 mg QD and /or HCTZ 25 mg with amiloride 2 to 5 mg QD	MC, OL, PRO, RCT Men and women, age 70-84 years with hypertension (SBP ≥180mm Hg or DBP ≥105 mm Hg or both)	N=6,614 4 years	Primary: Fatal stroke, fatal myocardial infarction, other fatal cardiovascular events Secondary: Blood pressure	Primary: The rate of prevention of cardiovascular deaths was similar in all groups (RR, 0.97 to 14; 95% CI, 0.86 to 1.26). Fatal cardiovascular events, including fatal stroke and fatal myocardial infarction, occurred in 19.8 per 1,000 patient-years in the β-blocker and/or HCTZ group, in the felodipine or isradipine group and in the enalapril or lisinopril group (RR, 0.99; 95% CI, 0.84 to 1.16). The relative risk of cardiovascular death in patients in the enalapril or lisinopril group as compared to the felodipine or isradipine group was 14 (95% CI, 0.86 to 1.26; P=0.67.) Secondary: Decreases in blood pressure were similar among the groups.
Borhani et al.[62] (1996)	DB, MC, positive-control, RCT	N=883	Primary: Rate of progression	Primary: There was no difference in the rate of progression of intimal-medial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
MIDAS Isradipine 2.5 to 5 mg BID vs HCTZ 12.5 to 25 mg QD	Patients, average of 58.5 years old, with hypertension	3 years	of intimal-medial thickness in carotid arteries Secondary: Rate of cardiovascular events (myocardial infarction, stroke, congestive heart failure, angina, sudden death), rate of non-major cardiovascular events and procedures (transient ischemic attacks, dysrhythmia, aortic valve replacement, femoral popliteal bypass graft), blood pressure	thickness between the treatment groups (P=0.68). Secondary: The rate of cardiovascular events was greater in the isradipine group than in the HCTZ group (5.65% vs 3.17%; P=0.07). The rate of non-major cardiovascular events was greater in the isradipine group than in the HCTZ group (9.05% vs 5.22%; P=0.02). There was a significant decrease in SBP in the HCTZ group as compared to isradipine (-19.5 vs -16.0 mm Hg; P=0.002). There was no difference in change in DBP (both groups -13.0 mm Hg).
National Intervention Cooperative Study[63] (1999) NICS-EH Nicardipine SR 20 mg BID vs trichlormethiazide	DB, RCT Patients age 60 years old and older with a SBP between 160 to 220 mm Hg and a DBP <115 mm Hg and no history of cardiovascular complications	N=414 5 years	Primary: Cardiovascular complications Secondary: Blood pressure, pulse, side effects, laboratory values	Primary: There was no difference in rate of cardiovascular complications during the study period (P=0.923). There was no difference in the number of patients experiences left ventricular hypertrophy on electrocardiogram (P=0.975). Secondary: Both groups experienced significant reductions in blood pressure from baseline (P=0.000). There was no significant difference in pulse rate between the groups. Side-effect rates did not differ between the groups (P=0.897).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2 mg QD				More patients in the trichlormethiazide group than in the nicardipine group had abnormal lab results at the end of the study; differences were significant for serum sodium levels (decreased in the trichlormethiazide group) and uric acid levels (increased with trichlormethiazide).
Lichtlen et al.[61] (1990) INTACT Nifedipine 80 mg QD vs placebo	DB, MC, PC, RCT Patients, age 65 years and younger, demonstrating early coronary artery disease who were not candidates for invasive therapeutic procedures	N=348 3 years	Primary: Progression of coronary artery disease detected on angiogram (change in minimal diameter, percent stenosis, transition into occlusion, new stenosis) Secondary: Critical clinical events (cardiac death, nonfatal myocardial infarction, unstable angina, need for procedure, heart failure, severe arrhythmias), progression of new lesions	Primary: In patients without study deviations, there were no significant differences in number of stenoses and occlusions per patient (nifedipine=3.7, placebo=3.88; P=0.437). The distribution among the arteries of the occlusions was not different between groups. The progression of stenosis was significant from baseline but changes were not significantly different between the groups (P<0.006 for all vs baseline; P>0.585 for group comparisons). Secondary: There was no difference between nifedipine treatment and placebo in number of critical events, 44 events in 24 patients receiving nifedipine vs 52 events in 35 patients in the placebo group (P=0.278). The nifedipine group had significantly fewer new lesions as compared to the placebo group: 78 (0.58 lesions/patients) vs 118 (0.8 lesions/patient) (P=0.031).
Brown et al.[65] (2000) INSIGHT Nifedipine 30 mg QD vs	DB, MC, PRO, RCT Patients, age 55 to 80 years old with hypertension (blood pressure ≥150/95 mm Hg or SBP ≥160 mm Hg) and	N=6,575 3 years	Primary: Composite death from any cardiovascular cause together with nonfatal stroke, myocardial infarction, or heart failure	Primary: There was no difference in composite cardiovascular deaths between the groups. Events occurred in 200 (6.3%) patients in the nifedipine group and 182 (5.8%) of the amiloride/HCTZ group (18.2 vs 16.5 events per 1,000 patient-years; P=0.34). Secondary: There was no difference in all-cause mortality (P=0.62), death from a vascular cause (P=0.67) and in nonfatal vascular events (P=0.50) between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amiloride 2.5 mg and HCTZ 25 mg QD (combination product) Doses were doubled or atenolol 25 to 50 mg or enalapril 5 to 10 mg was added.	at least 1 cardiovascular risk factor		Secondary: Total mortality, death from a vascular cause, nonfatal vascular event	the treatment groups.
Estacio et al.[68] (1998) ABCD Nisoldipine vs enalapril vs placebo Metoprolol or HCTZ was used if blood pressure goal was met.	DB, PRO, RCT Patients, age 40 to 74 years, with diabetes, with elevated blood pressure, (DBP >80 mm Hg)	N=470 67 months	Primary: Cardiovascular events	Primary: Patients in the enalapril group had significantly fewer cardiovascular events than the nisoldipine group including nonfatal myocardial infarctions (P =0.001), all myocardial infarctions (P =0.001), and all cardiovascular events (P=0.002).
Hypertension				
Sheehy et al.[42] (2000) Amlodipine 2.5 to 10 mg QD	RETRO Patients, age 65 years and older, with hypertension	N=7,818	Primary: Prescription renewal, drug switch rates, compliance rates,	Primary: Patients prescribed amlodipine had a greater compliance rate, 67.9%, than those prescribed felodipine 66.2% (P<0.01). Discontinuation rates were higher in the felodipine group by 27%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs felodipine 2.5 to 10 mg QD			office visits	Amlodipine treatment resulted in more continuous months of treatment (69.2), than felodipine treatment (57.8) (P<0.01). Renewal rates were significantly larger in the amlodipine group (89.0%), than the felodipine group (85.6%) (P<0.01). Switch rates were significantly larger, 5 times, in the felodipine group (10.2%) than the amlodipine group (1.9%) (P<0.01). Visits to specialists occurred significantly more in patients treated with amlodipine than felodipine, (OR, 1.14; 95% CI, 18 to 1.20).
Van der Krogt et al.[43] (1996) Amlodipine 5 to 10 mg QD vs felodipine ER 5 to 10 mg QD	DB, MC, PG, RCT Patients, age 18-75 years old, with mild to moderate hypertension (DBP ≥95 mm Hg and ≤114 mm Hg)	N=201 12 weeks	Primary: Number of responders (DBP ≤90 mm Hg after 12 weeks of monotherapy or decrease of >10 mm Hg if baseline DBP >100 mm Hg) who did not experience serious adverse events Secondary: Blood pressure, adverse events	Primary: Amlodipine treatment resulted in significantly more responders than felodipine treatment (P=0.046): 68% (69 of 101) of the amlodipine group were responders. 53% (49 of 92) of the felodipine group were responders. 32% (32 of 101) of the amlodipine group were not responders. 47% (43 of 92) of the felodipine group were not responders. Secondary: The decreases in SBP and DBP from baseline were significant within each group, but were similar between the groups (amlodipine SBP and DBP 12 weeks vs baseline; P<0.001, felodipine SBP and DBP 12 weeks vs baseline; P<0.001, amlodipine 12 week change vs felodipine 12 week change; P>0.05). Adverse events were experienced by 33% of the amlodipine group and 42% of the felodipine group. Significantly more patients in the felodipine group experienced serious adverse events (9 patients who experienced 17 serious events vs 2 patients who experienced 3 serious events; P=0.048).
Mounier-Vehier et al.[44] (2002)	DB, MC, PG RCT Men and women, age 60 years and	N=133 90 days	Primary: Mean difference in SBP from baseline to day 90	Primary: The decrease in SBP from baseline was significant within each group, but were similar between the groups (amlodipine day 90 vs baseline; P=0.0001, nicardipine day 90 vs baseline; P=0.0001, amlodipine 90 day

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 5 mg QD vs nicardipine 60 mg/daily, divided 2 to 3 times daily	older with isolated systolic hypertension (SBP= 160-208 mm Hg) and DBP <90 mm Hg		Secondary: Mean difference in DBP, pulse pressure, heart rate, percent of patients with normal blood pressure (<140/90 mm Hg), safety	change vs nicardipine 90 day change; P=0.38). Secondary: The decrease in DBP from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline; P=0.0001; nicardipine day 90 vs baseline; P=0.0003, amlodipine 90 day change vs nicardipine 90 day change; P=0.12). The decrease in pulse pressure from baseline was significant within each group but similar between the groups (amlodipine day 90 vs baseline, P=0.0001; nicardipine day 90 vs baseline, P=0.0001; amlodipine 90 day change vs nicardipine 90 day change, P=0.88). There was no difference between the groups in heart rate (P=0.60). At day 90, 25.9% and 23.4% of the amlodipine and nicardipine groups had achieved normal blood pressure (P=0.76). The numbers of people in each group reporting at least 1 adverse event were similar, 23 in the amlodipine group and 20 in the nicardipine group.
Kes et al.[45] (2003) Amlodipine 5 to 10 mg QD vs nifedipine 30 to 60 mg QD	MC, OL, RCT Patients with hypertension	N=155 12 weeks	Primary: Change in DBP	Primary: There was no significant difference in DBP between the amlodipine group and nifedipine group at 12 weeks (P=0.436).
Ryuzaki et al.[46] (2007) i-TECHO Amlodipine 2.5 to 10 mg QD	OL, RCT, XO Patients treated for hypertension (SBP >140 mm Hg or DBP >90 mm HG)	N=55 12 weeks (6 weeks per treatment)	Primary: Average home blood pressure readings, pulse rates, clinic blood pressure and pulse readings	Primary: The morning home SBP and DBP readings were lower in the nifedipine group than the amlodipine group (SBP 131±8 vs 133±10 mm Hg; P<0.05, DBP 80±8 vs 81±8 mm Hg; P<0.05). There were no significant differences in evening home blood pressure readings (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs nifedipine CR 20 to 80 mg QD				There was no significant difference in rates of achieving target blood pressure between the groups (P<0.05). Morning home pulse rates were greater in the nifedipine group than the amlodipine group (70±9 vs 69±9 beats/min; P<0.05). There were no significant differences between the groups in evening home pulse rates (P>0.05). The clinic SBP and DBP readings were significantly lower in the nifedipine group than in the amlodipine group (P<0.05). There were no significant differences between the groups in clinic pulse rates (P>0.05).
Saito et al.[48] (2007) ADVANCE-Combi Amlodipine 2.5 to 5 mg QD vs nifedipine CR 20 to 40 mg QD Valsartan 40 to 80 mg was added on if blood pressure goal not met.	DB, RCT Patients with untreated essential hypertension with sitting SBP ≥160 mm Hg or DBP ≥100 mm Hg; or previously treated with sitting SBP ≥150 mm Hg or DBP ≥95 mm Hg	N=514 16 weeks	Primary: Target blood pressure, achievement rate Secondary: Safety	Primary: Target blood pressure achievement rates were higher for the nifedipine treatment group than the amlodipine group (P<0.001). Patients in the amlodipine group were more likely to require additional treatment with valsartan or a dose increase of amlodipine (P<0.05). The reduction in blood pressure from baseline was greater in the nifedipine group (-34.0/-20.1) than in the amlodipine group (-27.0/-15.9; P<0.05). Secondary: Adverse event rates were not significantly different between the groups, 12.4% in the nifedipine group vs 7.6% of the amlodipine group (P=0.07).
Pepine et al.[49] (2003) CESNA-II	DB, DD, PG, MC, RCT Men and women	N=not specified 6 weeks	Primary: Change from baseline in DBP at 6 weeks	Primary: At 6 weeks, the mean SBP and mean DBP for the 2 treatment groups were not significantly different from each other and mean reductions in blood pressure were similar: amlodipine SBP/DBP 138/83 mm Hg, a decrease of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 5 to 10 mg QD vs nisoldipine ER 20 to 40 mg QD	with hypertension (DBP 90-109 mm Hg) and coronary artery disease		Secondary: Exercise duration, antihypertensive responder rate (% of patients with DBP <90 mm Hg), exercise test responder rate (increase in time by 20% and 60 seconds)	13/11 mm Hg, vs nisoldipine 137/81 mm Hg, a decrease of 15/13 mm Hg) (all P values not significant). Secondary: Both treatment groups experienced increases in exercise duration, increased by 21 seconds in the amlodipine group and 23 seconds in the nisoldipine group (P=0.268). Antihypertensive and exercise responder rates were similar between the groups (antihypertensive rates: 78% for amlodipine and 87% for nisoldipine; P>0.05 for both).
Whitcomb et al.[50] (2000) Amlodipine 2.5 to 10 mg QD vs nisoldipine ER 10 to 40 mg QD	DB, DD, MC, RCT Men and women, age 21 to 75 years, with hypertension	N=161 8 weeks	Primary: Between treatment comparison of change from baseline in DBP Secondary: Change from baseline in SBP, heart rate, percent of patients who responded	Primary: Treatment with amlodipine resulted in a significantly larger change from baseline in DBP (between-group difference 2.7 mm Hg; P=0.005). However, a pre-specified difference of greater than 5 mm Hg in least mean squares, here 1.1 to 4.3 mm Hg, showed that the treatments were similar in reduction of DBP. Secondary: Amlodipine treatment resulted in a significantly larger change from baseline in SBP than nisoldipine treatment (P value not reported, least mean square difference >5 mm Hg). At week 8, more patients in the amlodipine group were responders, 79%, as compared to the nisoldipine group, 60% (P=0.004).
White et al.[51] (2003) CESNA-III Amlodipine 5 to 10 mg QD vs nisoldipine ER 20	DB, MC, PRO, RCT African American patients with hypertension (blood pressure of 92 mm Hg to 114 mm Hg and SBP <200 mm Hg)	N=192 12 weeks	Primary: ABPM change from baseline in DBP in mean 24 hour period Secondary: ABPM change in SBP, awake and asleep blood pressure, changes	Primary: The decrease from baseline in DBP was similar between the groups: –16.0±2.3 mm Hg for nisoldipine and – 15.0±2.3 mm Hg for amlodipine (P=0.500). Secondary: The decrease from baseline in SBP was similar between the groups: –23.0±2.7 mm Hg for nisoldipine and –19.9±2.7 mm Hg for amlodipine (P=0.067). The changes from baseline in awake and asleep SBP and DBP were not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to 60 mg QD			in clinic blood pressure and pulse	significantly different between the groups except for awake SBP, for which the nisoldipine group had a larger reduction, –19.2 vs –15.9 mm Hg (P=0.045). The changes from baseline in clinic blood pressure and pulse were similar between the groups (P>0.05 for SBP and DBP; P=0.362).
Lenz et al.[52] (2001) Amlodipine 5 to 10 mg QD vs nisoldipine 10 to 20 mg QD	OL, XO Patients, 35 to 70 years old, with hypertension, (SBP 140-179 mm Hg and DBP 90-109 mm Hg), stable on amlodipine for at least 3 months prior to switch to nisoldipine	N=21 10 weeks	Primary: 24-hour ABPM	Primary: No significant difference in ABPM was found after patients switched from amlodipine to nisoldipine for the following: systolic nighttime, daytime and 24-hour blood pressure, diastolic nighttime and daytime blood pressure (P>0.05 for all). 24-hour DBP was significantly lower with amlodipine treatment than with nisoldipine treatment (75±10 vs 77v8.5 mm Hg; P=0.017).
Messerli et al.[78] (2002) Amlodipine-benazepril 5/10 mg to 5/20 mg QD	OL Patients ≥18 years with mild-to-moderate hypertension taking amlodipine 5-10 mg with inadequate BP (DBP ≥90 mm Hg, Group 1) or intolerance with amlodipine (DBP ≤90 mm Hg with edema, Group 2)	N=7,912 4 weeks	Primary: Change in mean sitting DBP (group 1), and percentage of patients whose edema improved (group 2) Secondary: Group 1-change in mean sitting SBP	Primary: In Group 1, mean reduction in DBP at week 4 was 11.5 mm Hg (95% CI, –11.8 to –11.3 mm Hg; P<0.001). Mean DBP declined from 96.5 (baseline) to 84.9 mm Hg (at 4 weeks). In Group 2, 85% of patients saw improvement in edema with 42% of patients experiencing complete resolution after receiving combination therapy (95% CI, 83% to 87%). Secondary: In Group 1, mean reduction in SBP at week 4 was 15.6 mm Hg (95% CI, –16.0 to –15.2 mm Hg; P<0.001).
Messerli et al.[79] (2000) <u>Study 1:</u> Amlodipine-	Two DB, MC, RCT Patients with uncomplicated essential	N=1,079 8 weeks	Primary: Change in DBP from baseline Secondary:	Primary: <u>Study 1</u> Significant reductions in DBP were observed with amlodipine/benazepril 5/10 mg and 5/20 mg (–9.4 and –9.7 mm Hg, respectively) compared to nifedipine 30 mg (–7.0 mm Hg; P<0.05) but not nifedipine 60 mg (–8.5;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
benazepril 5/10 mg to 5/20 mg QD vs nifedipine 30 to 60 mg/day Study 2: Amlodipine-benazepril 5/10 mg to 5/20 mg QD vs amlodipine 5 to 10 mg QD	hypertension who were 18-80 years of age		Change from baseline in SBP and heart rate	P>0.05). Study 2 Amlodipine/benazepril 5/10 mg (–8.9 mm Hg) and 5/20 mg (–9.1 mm Hg) produced significantly greater reductions in DBP than amlodipine 5 mg (–6.8 mm Hg; P<0.05) but not amlodipine 10 mg (–8.7 mm Hg; P>0.05). Secondary: Study 1 Significant reductions in SBP were observed only with amlodipine/benazepril 5/20 (–11.6 mm Hg) compared to nifedipine 30 mg (–7.9 mm Hg; P<0.05). Significantly less edema was reported with combination therapies (3.1% to 3.8%; P≤0.001) than nifedipine 60 mg (15.5%; P=0.008) but not nifedipine 30 mg (5.4%). Study 2 Significant reductions in SBP were observed only with amlodipine/benazepril 5/20 mg (–9.1 mm Hg) compared to amlodipine 5 mg (–5.3 mm Hg, P<0.05). There were no significant difference in SBP between amlodipine 10 mg and the combination therapies. Significantly less edema (P<0.001) was reported with amlodipine 5 mg (4.9%) and combination therapies (1.5% to 2.2%) compared to amlodipine 10 mg (23.6%).
Jamerson et al.[80] (2004) Amlodipine-benazepril 5/20 mg to 10/20 mg QD (fixed-dose combination) vs	DB, MC, PG, RCT Men and women 18-80 years with stage 2 hypertension	N=364 12 weeks	Primary: Percentage of patients with SBP reduction ≥25 mm Hg (if baseline <180 mm Hg) or ≥32 mm Hg (if baseline ≥180 mm Hg) Secondary:	Primary: Significantly more patients on combination therapy (74.2%) met the primary end point than with amlodipine monotherapy (53.9%; P<0.0001). The time by which 50% of patients attained the primary end point was 4 weeks shorter among patients randomized to combination therapy compared with those randomized to monotherapy (P<0.0001). Secondary: Significantly more patients on combination therapy met the DBP end point than amlodipine monotherapy (67.0% vs 48.3%; P=0.0003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5 to 10 mg QD			Percentage of patients with DBP ≥15 mm Hg (if baseline <110 mm Hg) or ≥20 mm Hg (if baseline ≥110 mm Hg), percentage of patients meeting goal of 140/90 mm Hg and ≤130/85 mm Hg, mean reduction in SBP and DBP and incidence of edema	Patients on combination therapy had significantly greater mean SBP reductions (–25.5 vs –20.5 mm Hg; P=0.0003) and DBP reductions (–14.3 vs –10.4 mm Hg; P=0.0001) than amlodipine monotherapy. Significantly more patients on combination therapy met the blood pressure goal of <140/90 mm Hg than amlodipine monotherapy (61% vs 43.3%; P=0.0007). Significantly more patients on combination therapy met the blood pressure goal of <130/85 mm Hg than amlodipine monotherapy (35.7% vs 19.1%; P=0.0004). The incidence of peripheral edema was significantly higher in the amlodipine monotherapy group (23.3% vs 12.6%; P=0.0102). There was no significant difference in the incidence of other adverse events.
Neutel et al.[81] (2005) SELECT Amlodipine-benazepril 5/20 mg QD vs amlodipine 5 mg QD vs benazepril 20 mg QD	DB, RCT Patients with stage 2 systolic hypertension	N=443 8 weeks	Primary: Reduction in SBP, proportion of patients achieving blood pressure control	Primary: Significantly greater SBP reductions were achieved with combination treatment compared to amlodipine or benazepril monotherapy (P<0.0001). Significantly more patients on combination therapy met blood pressure goals than on monotherapy (P<0.0001). No significant difference was noted in the incidence of adverse events. Adverse events were low in all 3 treatment arms, with less peripheral edema in the combination group than in the amlodipine-treated group.
Kuschnir et al.[82] (1996)	DB, MC, PC, PG, RCT	N=308	Primary: Reduction in mean	Primary: All treatment groups significantly reduced mean sitting DBP compared to

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Amlodipine-benazepril 5/20 mg QD (fixed-dose combination) vs amlodipine 5 mg QD vs benazepril 20 mg QD vs placebo	Men and women 21 to 80 years of age with uncomplicated primary hypertension	8 weeks	sitting DBP, SBP and percentage of patients with DBP <90 mm Hg or ≥10 mm Hg reduction	placebo (P<0.001). Combination amlodipine/benazepril had significantly greater reductions in DBP (–13.2 mm Hg; P<0.001) compared to amlodipine (–8.8 mm Hg) and benazepril (–6.7 mm Hg) monotherapy. Combination amlodipine/benazepril had significantly greater reductions in SBP (–24.7 mm Hg; P<0.001) compared to amlodipine (–16.2 mm Hg) and benazepril (–12.4 mm Hg). Significantly more patients on combination amlodipine/benazepril reached DBP <90 mm Hg or ≥10 mm Hg reduction (87.0%; P≤0.005) compared to amlodipine (67.5%) and benazepril (53.3%). Adverse events considered to be drug related occurred in 15.6% of patients receiving amlodipine/benazepril, 24.7% of patients receiving amlodipine, 6.5% of patients on benazepril and 11.7% of patients on placebo.
Chrysant et al.[83] (2007) Amlodipine-benazepril 10/40 mg QD for 6 weeks vs amlodipine-benazepril 10/40 mg QD for 2 weeks, then 20/40 mg QD for 4 weeks vs	DB, MC, RCT Men and women ≥18 years with mean sitting DBP ≥95 mm Hg not adequately controlled with amlodipine 10 mg/day monotherapy	N=812 6 weeks	Primary: Reduction in mean sitting DBP and SBP, reductions in ambulatory blood pressure, successful response (mean sitting DBP <90 mm Hg or decrease of ≥10 mm Hg from baseline), safety	Primary: Treatment with amlodipine/benazepril 10/40 mg and 10/20 mg resulted in a decrease of mean sitting SBP and DBP by 13.3/12.7 and 12.1/11.6 mm Hg, respectively, compared with monotherapy (6.6/8.5 mm Hg; P<0.0001). Amlodipine/benazepril 10/40 mg and 20/40 mg decreased ambulatory SBP and DBP by 9.9/6.7 and 7.4/5.2 mm Hg, respectively, compared with monotherapy (P<0.0001). Both combinations resulted in more responders than monotherapy (74% and 65% vs 54%; P<0.0001 and P<0.0085, respectively). Combination amlodipine and benazepril had significantly greater reductions in sitting SBP (–17 mm Hg; P<0.0001) compared to amlodipine monotherapy (–5 mm Hg). The incidence of pedal edema was lower but not significantly different in the amlodipine/benazepril combinations compared with monotherapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 10 mg QD for 6 weeks				(4.5%, 5.5% vs 9.2%, respectively; P=NS). No significant metabolic side effects were noted among the combination groups.
Chrysant et al.[84] (2004) Amlodipine-benazepril 5/40 mg QD for 4 weeks, then 10/40 mg QD for 4 weeks vs benazepril 40 mg QD for 8 weeks	DB, RCT Men and women (mean age 53 years) with mean sitting DBP ≥95 mm Hg not adequately controlled with benazepril 40 mg/day monotherapy	N=329 8 weeks	Primary: Reduction in mean sitting DBP and SBP, reduction in standing DBP and SBP, and change in heart rate, safety	Primary: Combination amlodipine and benazepril had significantly greater reductions in sitting SBP (–17 mm Hg; P<0.0001) compared to benazepril monotherapy (–5 mm Hg). Combination amlodipine and benazepril had significantly greater reductions in sitting DBP (–14 mm Hg; P<0.0001) compared to benazepril monotherapy (–7 mm Hg). Combination amlodipine and benazepril had significantly greater reductions in standing SBP (–17 mm Hg; P<0.0001) compared to benazepril monotherapy (–6 mm Hg). Combination amlodipine and benazepril had significantly greater reductions in standing DBP (–14 mm Hg; P<0.0001) compared to benazepril monotherapy (–7 mm Hg). No significant differences in heart rate were observed (P>0.05). No significant differences in adverse events were reported (P>0.05).
Fogari et al.[85] (1997) Amlodipine-benazepril 2.5/10 mg to 5/10 mg QD vs benazepril 10 mg QD	DB, MC, PC, RCT Men and women aged 24-73 years (mean 55 years) with hypertension inadequately controlled with ACE inhibitor monotherapy	N=448 8 weeks	Primary: Reduction in mean sitting DBP Secondary: Reduction in sitting SBP, standing DBP and SBP, and percentage of patients with DBP <90 mm Hg (deemed excellent response) or ≥10 mm Hg reduction	Primary: Significantly greater reductions in sitting DBP were observed with amlodipine/benazepril 2.5/10 mg (–5.3 mm Hg, 97.5% CI, –8.3 to –2.4 mm Hg; P=0.0001) and amlodipine/benazepril 5/10 mg (–4.5 mm Hg, 97.5% CI, –7.4 to –1.6 mm Hg; P=0.0006) compared to benazepril monotherapy. Secondary: Significantly greater reductions in sitting SBP were seen with amlodipine/benazepril 2.5/10 mg (–7.9 mm Hg, 97.5% CI, –12.3 to –3.5 mm Hg; P=0.0001) and amlodipine/benazepril 5/10 mg (–7.9 mm Hg, 97.5% CI, –12.2 to –3.6 mm Hg; P=0.0000) compared to benazepril monotherapy. Significantly greater reductions in standing DBP and SBP were also

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(deemed good response)	reported with the combination therapy compared to benazepril monotherapy (P≤0.001). Significantly more patients had excellent or good response with combination amlodipine/benazepril 2.5/10 mg (69.2%; P=0.0004) and 5/10 mg (65.8%; P=0.02) compared to benazepril monotherapy (40.5%). Tolerability was good in the 3 treatment groups and no significant abnormal laboratory data was detected.
Hilleman et al.[86] (1999) Amlodipine-benazepril (fixed-dose combination) vs monotherapy (atenolol, HCTZ, captopril, enalapril, lisinopril, amlodipine, diltiazem, nifedipine, verapamil)	MA Patients with mild-to-moderate essential hypertension	82 trials ≥4 weeks	Primary: Absolute change in supine DBP from baseline Secondary: Percent of patients who achieved BP control, safety	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine/benazepril, atenolol, lisinopril, and verapamil showed the greatest blood pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5% to 79.0%, with amlodipine/benazepril (74.3%) and lisinopril (79.0%) showing the highest percentage control (P=0.096). The incidence of adverse events ranged from 12.1% to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated significantly less overall side effects compared with nifedipine (P=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem (P=0.002). Although amlodipine/benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Jamerson et al.[88] (2007) ACCOMPLISH Amlodipine 5 mg	DB, MC, RCT Men and women >60 years with hypertension and cardiovascular or	N=10,704 Analysis performed at 6 months (complete trial	Primary: Changes in mean SBP from baseline to 6 months, blood pressure control rates (SBP/DBP	Primary: At baseline, 97% of subjects were treated with antihypertensive medications at entry but only 37% of participants had blood pressure control. Mean blood pressure fell from 145/80 to 132/74 mm Hg after 6 months of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD plus benazepril 20 mg QD vs benazepril 20 mg QD plus HCTZ 12.5 mg QD	renal disease or 2 target organs damaged by hypertension	duration 5 years)	<140/90 mm Hg or <130/89 mm Hg for patients with diabetes and chronic kidney disease)	treatment with either combination regimen (P<0.001). (This preliminary report did not compare the 2 treatment regimens.) The 6-month blood pressure control rate was 73% in the overall trial (78% in the United States), 43% in diabetics and 40% in patients with renal disease. Of the patients uncontrolled, 61% were not on maximal medications.
Malacco et al.[89] (2002) Amlodipine-benazepril 5/10 mg QD vs captopril-HCTZ 50/25 mg QD	DB, MC, RCT Patients with mild-to-moderate arterial hypertension (sitting DBP >95 mm Hg and/or SBP >160 mm Hg) inadequately controlled by monotherapy with an ACE inhibitor, calcium-channel blocking agent or diuretic	N=397 12 weeks	Primary: Reduction in sitting DBP and SBP Secondary: Percentage of patients responding to therapy (DBP<90 mm Hg, reduction in DBP ≥10 mm Hg or SBP ≥20 mm Hg, or SBP <150 mm Hg)	Primary: Significantly lower sitting DBP (–2.7 mm Hg; P<0.001) and SBP (–3.7 mm Hg; P<0.001) were achieved with amlodipine/benazepril compared to captopril/HCTZ. Secondary: Significantly more amlodipine/benazepril patients responded to therapy (94.8%) compared to captopril/HCTZ (86.0%; P=0.004). No differences in adverse events were reported between the 2 treatment groups.
Kereiakes et al.[90] (2007) Benazepril 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, then benazepril 20 mg/day plus amlodipine 5 mg/day for 4 weeks, then	DB, DD, MC, PG, RCT Patients with stage 2 hypertension (mean seated DBP ≥90 mm Hg but <115 mm Hg and SBP ≥160 mm Hg but <200 mm Hg or DBP ≥100 mm Hg but <115 mm Hg)	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining blood pressure goals of <140/90 mm Hg, <130/85 mm Hg,	Primary: Patients treated with olmesartan/HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril/amlodipine (least square mean change, –32.5 vs –26.5 mm Hg; P=0.024; least square mean treatment difference, –6.0 mm Hg; 95% CI, –11.1 to –0.8 mm Hg). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan/HCTZ compared with benazepril/amlodipine at week 12 (P=0.056). The percentage of patients achieving goal rates at the end of the study for

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benazepril 20 mg/day plus amlodipine 10 mg/day for 4 weeks vs olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan-HCTZ 40/12.5 mg/day (fixed-dose combination) for 4 weeks increased to 40/25 mg for 4 weeks			and <130/80 mm Hg	olmesartan/HCTZ and benazepril/amlodipine were 66.3% and 44.7% (P=0.006) for <140/90 mm Hg, 44.9% vs 21.2% (P=0.001) for <130/85 mm Hg, and 32.6% and 14.1% (P=0.006) for <130/80 mm Hg.
Tatti et al.[59] (1998) FACET Amlodipine 10 mg QD vs fosinopril 20 mg QD If blood pressure was not controlled on monotherapy, the other study	OL, PRO, RCT Men and women, diagnosed with hypertension (SBP >140 mm Hg or DBP >90 mm Hg) and non-insulin dependent diabetes	N=380 Up to 3.5 years	Primary: Blood pressure Secondary: Fasting serum glucose, serum creatinine, plasma insulin, $HbA1_c$, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fibrinogen, microalbuminuria	Primary: Both treatment groups significantly lowered SBP and DBP from baseline (P<0.05). SBP was lower in the amlodipine group by 4 mm Hg than in the fosinopril group (P<0.01). There was no difference in DBP, both groups decreased by 8 mm Hg. Amlodipine was added by 30.7% of the fosinopril group and fosinopril was added by 26.2% of the amlodipine group (P>0.1). Secondary: No difference between the groups was found for serum creatinine, $HbA1_c$, and triglycerides at the endpoint (P>0.05). Fasting serum glucose, serum insulin and microalbuminuria were significantly lower at endpoint for both groups but not significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
drug was added.				different from each other (P>0.05). Total cholesterol increased in both groups, and high-density lipoprotein cholesterol increased significantly in the fosinopril group (P<0.05). No difference in fibrinogen levels was observed between the groups at the end of the trial (P>0.05).
Miranda et al.[100] (2008) Amlodipine 2.5 to 10 mg and ramipril 2.5 to 10 mg QD vs amlodipine 2.5 to 10 mg QD	MC, DB, AC, RCT Adults 40 to 79 years of age with stage 1 or 2 essential hypertension	N=222 18 weeks	Primary: Change in SBP and DBP Secondary: Safety and tolerability	Primary: The mean changes in ambulatory BP were greater with amlodipine and ramipril compared to amlodipine monotherapy (SBP, -20.21 vs -15.31 mm Hg and DBP, -11.61 vs -8.42 mm Hg, respectively; both, P=0.002]. There was no significant difference among the treatment groups in office BP (SBP, -26.60 vs -22.97 mm Hg and DBP, -16.48 vs -14.48 mm Hg; both, P=NS). Twenty-nine patients (22.1%) treated with combination therapy and 41 patients (30.6%) treated with monotherapy experienced ≥1 adverse event considered possibly related to study drug. The combination-therapy group had lower prevalence of edema (7.6% vs 18.7%; P=0.011) and a similar prevalence of dry cough (3.8% vs 0.8%; P=NS).
Fogari et al.[53] (2007) CANDIA Amlodipine 10 mg once QD vs candesartan 16 mg and HCTZ 12.5 mg QD	DB, MC, RCT Patients, 20 to 80 years old, with mild to moderate uncomplicated hypertension not controlled on monotherapy with an antihypertensive (agents not listed), (SBP <180 mg Hg and DBP 90 to 110 mg Hg)	N=203 8 weeks	Primary: Decrease in DBP Secondary: Sitting SBP, reduction of the orthostatic blood pressure, change in heart rate, percentage of patients normalized (DBP <90 mm Hg and SBP <140 mm Hg), percentage of responders (reduction in DBP	Primary: There was no significant difference in the mean decrease in DBP between treatment groups; the difference in final DBP was -0.02 mm Hg (95% CI, -1.48 to 1.52 mm Hg; P=0.979). Secondary: There was no significant difference between the groups at week 8 for the following: sitting SBP (P=0.835), heart rate (P<0.500), orthostatic SBP (P=0.883), orthostatic DBP (P=0.264), percentage of patients normalized (P=10), percentage of responders (P=0.900). The number of patients reporting an adverse event was greater in the amlodipine group (P=0.001). The number of patients reporting an adverse drug-related event was greater in the amlodipine group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			≥5 mm Hg)	Changes in blood chemistry and other secondary measurements were not significantly different between the treatment groups.
Ribeiro et al.[55] (2007) LAMHYST Amlodipine 5 to 10 mg QD vs losartan 50 to 100 mg QD	DB, PG, PRO, RCT Males and females, age 18-79 years old, with diagnosis of mild (>95 mm Hg but <115 mm Hg) to moderate essential hypertension and not taking an antihypertensive medication (within last 4 weeks)	N=194 12 weeks	Primary: Difference between treatment groups in mean change in ABPM for last 9 hours of treatment and during drug holiday	Primary: After 12 weeks, mean reductions in SBP were significantly larger in the amlodipine group than the losartan group (–18.1 vs –10.1 mm Hg; P<0.001). Mean reductions in DBP were significantly larger in the amlodipine group than the losartan group (–18.1 vs –10.1 mm Hg; P<0.05). Mean increases in SBP were similar between the groups during the 2-day drug holiday (P>0.05). After the 2-day drug holiday, SBP was lower than baseline in both groups (P<0.001), with the amlodipine group SBP remaining significantly lower (P<0.01). Mean increases in DBP were similar between the groups during the 2-day drug holiday (P>0.05). After the 2-day drug holiday, DBP was lower than baseline in both groups (P=0.0001), with the amlodipine group DBP remaining significantly lower (P<0.05).
Oparil et al.[103] (1996) Amlodipine 5 to 10 mg QD vs losartan 50 to 100 mg QD If goal DBP (≤90 mm Hg) was not attained, drug doses could be doubled and/or HCTZ mg was	DB, DD, MC, RCT Patients with hypertension	N=900 12 weeks	Primary: Efficacy, tolerability, effects on quality of life	Primary: DBP reductions after 4, 8, and 12 weeks of therapy were clinically comparable (losartan group: 7.3, 10.4, and 11.1 mm Hg, respectively; amlodipine group: 7.9, 11.2, and 11.8 mm Hg, respectively; P=NS). Similar reductions in SBP were seen for both treatment groups (P value not significant). The percentage of patients reaching goal DBP (≤90 mm Hg) or DBP ≥90 mm Hg with a ≥10 mm Hg decrease from baseline) was comparable for the two groups, with 68% of patients in the losartan group and 71% of patients in the amlodipine group reaching goal. Significantly more patients in the amlodipine group had drug-related adverse experiences (27% vs 13%; P=0.029). Edema was more common in patients receiving the amlodipine regimen than in those receiving the losartan regimen (11% vs 1%; P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
added.				Overall quality of life was not different in the 2 treatment groups.
Chrysant et al.[56] (2008) COACH Amlodipine 5 to 10 mg QD and olmesartan 10 to 40 mg vs amlodipine 5 to 10 mg QD vs olmesartan 10 to 40 mg QD vs placebo	DB, MC, PC, RCT Patients ≥ 18 years of age with essential hypertension (seated DBP ≥95and <120 mm Hg)	N=1,940 8 weeks	Primary: Change from baseline in seated DBP at week 8 Secondary: Change from baseline in seated SBP at week 8, mean change from baseline in seated DBP and SBP at weeks 2, 4, 6 and 8 without last observation carried forward, proportion of patients achieving BP goal (<140/90 mm Hg or <130/80 mm Hg), safety	Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week 8 (P<0.001). Reductions in seated DBP with monotherapy treatment ranged from –8.3 to –12.7 mm Hg; reductions with combination therapy ranged from –13.8 to –19.0 mm Hg. All combinations reduced seated DBP significantly greater than either component as monotherapy at the same dosage (P<0.001). Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week 8 (P<0.001 for treatment, P=0.024 for placebo). All combinations reduced seated SBP significantly greater either component as monotherapy at the same dosage (P<0.001). The proportion of patients achieving goal BP were: 20.0% to 36.3% of patients receiving olmesartan monotherapy 21.1% to 32.5% of patients receiving amlodipine monotherapy 35.0% to 53.2% of patients receiving combination therapy 8.8% of patients receiving placebo. Combination therapy resulted in significantly greater achievement of goal BP than monotherapy (P<0.005). No difference in overall rates of adverse events across the different treatment groups was seen. Nearly 27% of patients experienced a drug-related adverse event. Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment: none of the changes were considered clinically significant. Platelet counts increased significantly from baseline (statistically) for patients receiving amlodipine, however the increase was <10% and not deemed clinically relevant.
Chrysant et al.[113] (2009)	OL, ES Patients ≥ 18 years	N=1,684 44 weeks OL	Primary: Reduction in mean seated systolic	Primary: SeDBP decreased from 101.5 mm Hg at baseline to 81.9 mm Hg and mean SeSBP decreased from 163.6 mm Hg at baseline to 131.2 mm Hg at week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
COACH Amlodipine 5 to 10 mg QD and olmesartan 10 to 40 mg HCTZ 12.5 to 25 mg could be added if BP was not controlled (<140/90 mm Hg or <130/80 mm Hg in patients with diabetes).	of age with essential hypertension (seated DBP ≥95and <120 mm Hg)	therapy (52 weeks total study duration including 8 week DB phase)	BP (SeSBP) and seated diastolic BP (SeDBP), change in SeSBP and SeDBP, percentage of patients achieving BP goal (<140/90 mm Hg or <130/80 mm Hg for patients with diabetes)	52. Approximately 31% of patients remained on amlodipine 5 mg and olmesartan 40 mg. Increasing the dose of amlodipine to 10 mg in combination with olmesartan 40 mg produced further decreases in mean SeDBP of 4.8 mm Hg and mean SeSBP of 7.3 mm Hg. Addition of HCTZ 12.5 mg to amlodipine 10 mg and olmesartan 40 mg decreased mean SeDBP by 4.5 mm Hg and mean SeSBP by 7.7 mm Hg. Doubling the HCTZ dose from 12.5 to 25 mg decreased mean SeDBP and mean SeSBP by an additional 6.0 mm Hg and 9.9 mm Hg, respectively. Patients who received the triple therapy had the greatest mean SeSBP reduction (36.1 mm Hg). Approximately 67% of patients achieved BP goal by week 52. The BP goal achievement was 80% for amlodipine+olmesartan 5/40 mg, 70.6% for amlodipine+olmesartan 10/40 mg, 66.6% for amlodipine+olmesartan+HCTZ 10/40/12.5 mg, and 46.3% for amlodipine+olmesartan+HCTZ 10/ 40/25 mg. The addition of HCTZ 25 mg enabled more patients to achieve BP targets of <140/90 mm Hg (77.7%), <130/85 mm Hg (47.5%), and <130/80 mm Hg (36.4%) compared with the other treatment regimens. No major safety issues emerged with long-term therapy. The frequency of edema ranged from 8.9% in patients treated with amlodipine 5 mg and olmesartan 40 mg to 14.5% in patients treated with amlodipine 10 mg and olmesartan 40 mg plus HCTZ 25 mg. Other TEAEs experienced by ≥3% of patients included upper respiratory tract infection (6.5%), nasopharyngitis (5.2%), extremity pain (4.1%), sinusitis (3.6%), arthralgia (3.3%), and back pain (3.1%). headache (2.0%), hypotension (1.8%), and fatigue (1.6%). The incidence of cough was 0.4%.
Maciejewski et al.[57] (2006) Amlodipine 5 to 10 mg QD	DB, PRO, RCT, XO African-Americans, older than 35 years, with baseline blood pressure >140/90	N=20 8-10 weeks for each arm with 2 week washout	Primary: Comparison of 24 hour ABPM recordings Secondary:	Primary: There was no difference between the groups based on 24 hour ABPM: SBP amlodipine 130±8 vs valsartan 127±17 (P=0.350) and DBP amlodipine 82±5 vs valsartan 84±16 (P=0.430). Secondary:

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vs valsartan 80 to 160 mg QD For all patients: if blood pressure exceeded 140/90 while on highest treatment dose, HCTZ 12.5mg/day was added to the regimen.	mm Hg and not on antihypertensive treatment	period before crossover	Magnitude of change from baseline in SBP and DBP with each treatment, percent of patients who achieved goal <140/<90 with each treatment based on clinic blood pressure measurements	There was no difference between groups in magnitude of change from baseline in blood pressure (amlodipine -25±8/-18±7 vs valsartan -25±9/-16±7; P=0.61), and in percent of patients achieving goal blood pressure, 70% in the valsartan group and 75% in the amlodipine group (P=0.62).
Ichihara et al.[58] (2006) Amlodipine 2.5 to 10 mg QD vs valsartan 40 to 160 mg QD	RCT Patients with untreated hypertension (clinic SBP >140 mm Hg and/or DBP >90 mm Hg; or ABPM SBP >135 mm Hg and/or DBP >98 mm Hg)	N=100 12 months	Primary: ABPM and clinic blood pressure Secondary: Pulse wave velocity, carotid intima-media thickness, urinary albumin excretion	Primary: Both treatments resulted in significant decreases in blood pressure, both ambulatory and clinic, over 12 months from baseline; blood pressure decreases were similar between treatment groups (Between treatments: clinic SBP P=0.34; clinic DBP P=0.85; 24 hour ABPM P=0.14). Blood pressure variability decreased significantly in the amlodipine group compared to the valsartan group, where there was no change in blood pressure variability (P<0.01). Secondary: The decrease in pulse wave velocity was significant from baseline for both groups, but not significantly different from each other (P<0.05 from baseline). Intima-media thickness was not changed significantly from baseline for either treatment (P>0.05 for both from baseline). Urinary albumin excretion in the valsartan group decreased significantly both from baseline and compared to amlodipine treatment (P<0.05 from baseline, P value for comparison not reported).
Philipp et al.[76] (2007)	DB, MC, PC, RCT	N=1,911	Primary: Mean sitting DBP	Primary: All treatments significantly decreased mean sitting DBP from baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
<u>Study 1</u> Amlodipine 2.5 to 5 mg and valsartan 40 to 320 mg QD vs amlodipine 2.5 to 5 mg QD vs valsartan 40 to 320 mg QD vs placebo	Males and females, ages 18 years and older with hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	8 weeks	Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 2)	(P<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (P<0.05 for all combinations compared to respective doses of monotherapy except amlodipine 2.5 mg and valsartan 40 mg QD). Secondary: All treatments significantly decreased mean sitting SBP from baseline (P<0.05). Combination treatment resulted in significantly greater blood pressure reduction than either monotherapy (P<0.05 for all combinations compared to respective doses of monotherapy). Response rates were significantly different from placebo for all treatment groups (P<0.05). Response rates for combination products were significantly different than each monotherapy for the following combinations: amlodipine 5 mg plus valsartan 80 mg, amlodipine 5 mg plus valsartan 40 mg and amlodipine 2.5 mg plus valsartan 80 mg (P<0.05 for each combination compared to both monotherapy). Response rates for all combinations produced significantly improved compared to either one of the monotherapies except amlodipine 2.5 mg plus valsartan 40 mg (P<0.05 for each combination compared to one of the respective monotherapy). Control rates with therapy were significantly better than placebo, with the highest control rate achieved with amlodipine 5 mg plus valsartan 320 mg (P<0.05 compared to placebo, P value not reported for others). Adverse event rates were not significantly different among combination treatment, amlodipine treatment, and placebo. Adverse event rates were significantly different between amlodipine plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				valsartan and valsartan monotherapy (P<0.05). The most commonly reported adverse events for combination treatment were: peripheral edema, headache, nasopharyngitis, upper respiratory tract infection and dizziness. Peripheral edema occurred significantly less frequently in the combination treatment group than the amlodipine monotherapy group (5.4% vs 8.7%; P=0.014) and significantly more frequently than in the valsartan monotherapy group (5.4% vs 2.1%; P<0.001). Peripheral edema occurrence in the valsartan group was similar to the rate in the placebo group.
Philipp et al.[76] (2007) Study 2 Amlodipine 10 mg and valsartan 160 or 320 mg QD vs amlodipine 10 mg QD vs valsartan 160 to 320 mg QD vs placebo	DB, MC, PC, RCT Male and females, ages 18 years and older with hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=1,250 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events (combined with study 1)	Primary: Mean sitting DBP was significantly reduced for both combination as compared to the individual components and to placebo (P<0.05). Secondary: Response rates and control rates for combination treatments were significantly greater than valsartan monotherapy therapy and placebo therapy, but not different from amlodipine monotherapy (P<0.05). Adverse event rates were not significantly different between combination treatment, amlodipine treatment and placebo. Adverse event rates were significantly different between amlodipine plus valsartan and valsartan monotherapy (P<0.05).
Schunkert et al.[111] (2009) Amlodipine-valsartan 10/160 mg QD	RCT, MC, DB, AC Patients ≥18 years of age with mild-to-moderate essential hypertension (mean	N=944 8 weeks	Primary: Change from baseline in mean sitting diastolic BP (msDBP)	Primary: At week 8, a significantly greater reduction from baseline in msDBP was observed with amlodipine/valsartan (11.4 mm Hg) compared to amlodipine monotherapy (9.3 mm Hg; P<0.0001). Secondary:

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vs amlodipine 10 mg QD	sitting diastolic blood pressure (msDBP) ≥90 mm Hg and <110 mm Hg) who were inadequately controlled on amlodipine 10 mg		Secondary: Change from baseline in mean sitting systolic blood pressure (msSBP), responder rate (msDBP <90 mm Hg or ≥10 mm Hg reduction from baseline) and DBP control rate (msDBP <90 mm Hg)	At week 8, a significantly greater reduction from baseline in msSBP was observed with amlodipine/valsartan (12.9 mm Hg) compared to amlodipine monotherapy (10.0 mm Hg; P<0.0001). The mean reductions in msSBP/msDBP were 24.4/17.2 mm Hg and 21.6/15.0 mm Hg for the amlodipine/valsartan and amlodipine monotherapy, respectively The responder rate was significantly greater with amlodipine/valsartan (79.0%) than with amlodipine monotherapy (70.1%; P=0.0011). The percentage of patients with controlled DBP was significantly higher with amlodipine/valsartan (77.8%) compared to amlodipine monotherapy (66.5%; P<0.0001). The incidence of peripheral edema was higher with amlodipine monotherapy (9.4%) compared to amlodipine/valsartan (7.6%).
Ke et al.[108] (2010) Amlodipine-valsartan 5/80 mg QD (fixed-dose combination) vs amlodipine 5 mg QD	RCT, MC, DB, AC Hypertensive patients 18 to 86 years of age with mean sitting diastolic BP ≥95 and <110 mm Hg who were inadequately controlled on amlodipine 5 mg for 4 weeks	N=698 8 weeks	Primary: Change in mean sitting diastolic BP (msDBP) Secondary: Change in mean sitting systolic BP (msSBP), diastolic response rate (msDBP <90 mm Hg or ≥10 mm Hg decrease from baseline), diastolic control rate (msDBP <90 mmHg) and overall BP control rate (msSBP/msDB <140/90 mmHg)	Primary: At week 8, the reduction in msDBP was greater with amlodipine/valsartan (11.4/9.7 mm Hg) than with amlodipine (7.4/7.1 mm Hg; P<0.0001). Secondary: At week 8, the diastolic control and response rates were significantly greater in the amlodipine/valsartan compared to amlodipine monotherapy (diastolic control, 75.5% vs. 64.5%; P=0.0002 and response rates, 79.3% vs. 66.8% (P<0.0001), respectively). The proportion of patients achieving overall BP control was greater in the amlodipine/valsartan group compared to amlodipine monotherapy (69.2% vs. 57.6%, P=0.0013). More than 50% of patients not adequately controlled on amlodipine monotherapy achieved BP control after 2 weeks of therapy with amlodipine/valsartan. In a subgroup of patients, there was a significant reduction in 24-h mean BP from baseline with amlodipine/valsartan (-7.3/-6.3 mm Hg; P<0.0001). There was no significant difference with amlodipine from baseline (-0.2/+0.3 mm Hg; P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Destro et al.[107] (2008) Ex-EFFeCTS Amlodipine-valsartan 5/160 mg QD for 2 weeks, then 10/160 mg QD for 6 weeks vs amlodipine 5 mg QD for 2 weeks, then 10 mg QD for 6 weeks HCTZ 12.5 mg could be added at week 4 if MSSBP was ≥130 mm Hg.	RCT, DB, MC Patients ≥18 years f age with stage 2 hypertension (mean sitting systolic blood pressure ≥160 mm Hg)	N=646 8 weeks	Primary: Mean changes in mean sitting SBP (MSSBP) at week 4 Secondary: Change from baseline in mean sitting DBP (MSDBP) at week 4, change in mean sitting BP at weeks 2, 4, and 8, and overall BP control rate at week 8 (MSSBP/MSDBP <140/90 mm Hg)	Primary: At week 4, reductions in MSSBP were significantly greater in patients receiving amlodipine/valsartan (30.1 mm Hg) than in those receiving amlodipine (23.5 mm Hg; P<0.0001). At week 4, MSSBP reductions in patients with baseline MSSBP ≥180 mm Hg were greater for amlodipine/valsartan (40.1 mm Hg) than for those receiving amlodipine (-31.7 mm Hg; P=0.0018). Secondary: At week 4, reductions in MSDSBP were significantly greater in patients receiving amlodipine/valsartan (12.5 mm Hg) than in those receiving amlodipine (8.6 mm Hg; P<0.0001) and all other time points (data not provided). At week 4, 45.3% of patients were controlled on amlodipine/valsartan compared with 23.8% on amlodipine monotherapy. At week 8, corresponding control rates were 53.0% and 31.1%, respectively (P<0.0001)..
Flack et al.[112] (2009) EX-STAND Amlodipine-valsartan 5/160 mg QD for 2 weeks, then 10/160 mg QD for 10 weeks (A/V) vs amlodipine 5 mg	RCT, DB, MC, AC Black patients ≥18 years of age with stage 2 hypertension (mean sitting systolic BP ≥160 and <200 mm Hg	N=572 12 weeks	Primary: Change in mean sitting systolic BP (MSSBP) from baseline to week 8 Secondary: Change in mean sitting diastolic BP (MSDBP) from baseline to week 8, change from baseline in MSSBP and MSDBP after 2, 4, 8 and 12	Primary: At week 8, treatment with amlodipine/valsartan significantly decreased MSSBP (33.3 mm Hg) compared to amlodipine monotherapy (26.6 mm Hg; P<0.0001). Secondary: Amlodipine/valsartan produced significantly greater reductions in MSDBP from baseline compared with amlodipine monotherapy throughout the study: week 2 (9.7 vs 6.9 mm Hg; P=0.0001), week 4 (13.2 vs 10.7 mm Hg; P=0.0008), week 8 (14.0 vs 11.2 mm Hg; P=0.0002), and week 12 (16.1 vs 12.8 mm Hg; P<0.0001). At week 8, 49.8% of patients in the amlodipine/valsartan group and 30.2% in the amlodipine monotherapy group had their BP controlled to <140/90 mm Hg (OR, 2.4; P<0.0001). At week 12, 57.2% of patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD for 2 weeks, then 10 mg QD for 10 weeks (A) If SBP was ≥130 mm Hg at week 4, A/V could be titrated to 10/320 mg dose. At week 8, HCTZ 12.5 mg was optionally added to both A/V and A if SBP ≥130 mm Hg.			weeks of treatment, BP control (<140/90mmHg) after 12 weeks of therapy	amlodipine/valsartan group and 35.9% in the amlodipine monotherapy group attained BP <140/ 90 mm Hg (OR, 2.5; P<0.0001).
Schrader et al.[109] (2009) Amlodipine-valsartan 5/160 mg QD (fixed-dose combination) for 12 weeks vs amlodipine 10 mg QD for 8 weeks, then amlodipine-valsartan 5/160 mg QD (fixed-dose combination) for 4 weeks	RCT, DB, MC Hypertensive patients who were ≥55 years of age with mean sitting systolic BP ≥130 and ≤160 mm Hg who were inadequately controlled on amlodipine 5 mg for 4 weeks	N=1,183 12 weeks	Primary: Change in mean sitting systolic BP (MSSBP) Secondary: Change in MSSBP and mean sitting diastolic BP (MSDBP), SBP control rate (MSSBP <130 mm Hg), overall BP control rate (BP <140/90 mm Hg for nondiabetic patients and <130/80 mm Hg for diabetic patients), and SBP response (MSSBP <130 mm Hg or ≥20 mm Hg	Primary: At week 8, there was a greater reduction in MSSBP with amlodipine/valsartan (-8.01 mm Hg) than with amlodipine (-5.95 mm Hg; P<0.001 for non-inferiority and P=0.002 for superiority). Secondary: Non-inferiority was also observed at week 4 (-8.29 vs. -6.29; P<0.001) and week 8 (-8.23 vs. -6.13; P<0.001) in MSSBP, at week 4 (-5.02 vs. -4.23; P<0.001) and week 8 (-4.70 vs. -4.06; P<0.001) in MSDBP, and at week 12 after the switch from amlodipine to amlodipine/valsartan (-9.13 vs. -8.16; P<0.001 for MSSBP and -5.52 vs. -4.90; P<0.001 for MSDBP). Systolic control with amlodipine/valsartan was greater than with amlodipine at week 4 (34.98% vs. 24.83%; P<0.001) and week 8 (34.28% vs. 26.21%; P=0.019), and similar after the switch from amlodipine 10 mg to amlodipine/valsartan at week 12 (38.04% vs. 31.81%;P=0.162). Systolic BP response rates were higher with amlodipine/valsartan than with amlodipine at week 4 (37.20% vs. 26.72%, P<0.001) and week 8 [36.57% vs. 27.77%; P=0.009), and similar after the switch from amlodipine to amlodipine/valsartan at week 12 (40.36% vs. 35.76%; P=0.347).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			reduction from baseline)	The incidence of peripheral edema was significantly lower with amlodipine/valsartan than with amlodipine (6.6% vs. 31.1%, P<0.001). Peripheral edema resolved in 56% patients who switched from amlodipine amlodipine/valsartan without the loss of effect on BP reduction.
Sinkiewicz et al.[110] (2009) Amlodipine-valsartan 10/160 mg or 5/160 mg QD vs valsartan 160 mg QD	RCT, DB, MC, AC Patients ≥18 years of age with essential hypertension (mean sitting diastolic BP ≥90 mm Hg and <110 mm Hg) who were inadequately controlled on valsartan 160 mg	N=947 8 weeks	Primary: Change from baseline in mean DBP Secondary: Change from baseline in mean sitting systolic blood pressure (SBP), responder rate (mean DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), and DBP control rate (mean DBP < 90 mm Hg)	Primary: At week 8, a significantly greater reduction in mean DBP was observed with both amlodipine/valsartan combinations (10/160 mg: -11.5 mm Hg, 5/160 mg: -9.6 mm Hg; both P<0.0001) compared to valsartan monotherapy (-6.7 mm Hg). Secondary: At week 8, a significantly greater reduction in mean SBP was observed in both amlodipine/valsartan combinations (10/160 mg: -14.3 mm Hg, 5/160 mg: -12.2 mm Hg; both P<0.0001) compared to valsartan monotherapy (-8.3 mm Hg). Overall mean SBP/DBP reductions of 22.5/15.5 mm Hg and 21.3/13.7 mm Hg were observed in the amlodipine/valsartan 10/160 mg and 5/160mg treatment groups, respectively compared with 16.7/11.4 mm Hg in the valsartan 160 mg group. The amlodipine/valsartan 10/160 mg combination showed a significantly greater reduction in mean SBP/DBP compared to amlodipine/valsartan 5/160 mg (P<0.001). Responder rates were higher in both amlodipine/valsartan groups (10/160 mg: 81% [P<0.0001]; 5/160 mg: 68% [P=0.0018], respectively) compared to valsartan monotherapy (57%). Peripheral edema was the most frequent adverse event, which was reported in 9.1% of patients receiving amlodipine/valsartan (10/160 mg), 0.9% of patients receiving amlodipine/valsartan (5/160 mg), and 1.3% of patients receiving valsartan monotherapy.
Poldermans et al.[77] (2007) Amlodipine 5 to 10 mg QD and valsartan 160 mg	AC, DB, MC, PG, RCT Males and females, ages 18 years and older with	N=130 6 weeks	Primary: Safety/adverse events, vital signs, hematology, biochemistry variables	Primary: Both treatments were well tolerated, 26 (40.6%) of patients receiving amlodipine and valsartan and 21 (31.8%) of patients receiving lisinopril and HCTZ reported an adverse events and most were not considered drug related.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD vs lisinopril 10 to 20 mg and HCTZ 12.5 mg QD	hypertension (mean DBP ≥110 mm Hg and <120 mm Hg)		Secondary: Efficacy (mean DBP, response rate, proportion of patients with mean DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline)	Peripheral edema was reported more often in the amlodipine and valsartan group than the lisinopril and HCTZ group (7.7% vs 1.5%) and cough was reported less often in the amlodipine and valsartan group than the receiving lisinopril and hydrochlorothiazide group (1.6% vs 3.0%). No difference was found between the treatments in changes in laboratory values or biochemistry variables. Secondary: Both treatments led to a reduction in mean SBP and DBP (P<0.0001 for both from baseline) but were not significantly different from each other. Mean blood pressure for each group at study end: amlodipine and valsartan 135.0/83.6 mm Hg and lisinopril and HCTZ 138.7/85.2 mm Hg. The response rate was similar among the groups (100% vs 95.5%; P=NS).
Calhoun et al.[95] (2009) Amlodipine-valsartan-HCTZ 10/320/25 mg QD vs valsartan-HCTZ 320/25 mg QD vs amlodipine-valsartan 10/320 mg QD vs amlodipine-HCTZ 10/25 mg QD	DB, MC, RCT Patients 18 to 85 years of age with moderate to severe essential hypertension	N=2,271 8 weeks	Primary: Difference in mean sitting diastolic blood pressure and mean sitting systolic blood pressure.	Primary: At each assessment after week 3, a significantly greater proportion of patients receiving triple therapy achieved overall BP control (<140/90 mm Hg) compared with those receiving any of the dual therapies (all P<0.0001). At end point, 70.8% of patients in the triple-therapy group achieved control, compared with 48.3% for valsartan/HCTZ, 54.1% for amlodipine/valsartan, and 44.8% for amlodipine/HCTZ (all P<0.0001). Triple therapy with amlodipine/valsartan/HCTZ improved BP control significantly better than any of the dual therapies.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pareek et al.[99] (2010) Amlodipine 2.5 to 5 mg and atenolol 25 to 50 mg QD vs atenolol 25 to 50 mg QD	MC, AC, OL, RCT Adults with either untreated or pretreated essential hypertension	N=190 12 weeks	Primary: Change in SBP and DBP	Primary: At the end of four weeks, the mean change in SBP (-30.0 ± 10.4 vs -25.08 ± 9.05; P=0.008) and DBP (-18.10 ± 7.45 vs -14.78 ± 7.48; P=0.021) was significantly greater in the low-dose combination therapy as compared with the low-dose monotherapy. At the end of 12 weeks, the mean SBP (127.82 ± 8.90 vs 138.0 ± 14.4; P=0.001) and mean DBP (81.73 ± 8.78 vs 87.35 ± 5.50; P=0.011) were significantly lower in the high-dose combination group as compared with the high-dose monotherapy group.
Gustin et al.[47] (1996) Felodipine 5 to 10 mg QD vs nifedipine 30 to 60 mg QD	XO Patients with hypertension, stable on nifedipine for at least 3 months were switched to felodipine	N=127 2 months	Primary: Blood pressure Secondary: Side effects and use of supplemental antihypertensive agents	Primary: There was no difference in SBP before and after switching agents. However, there was a difference in DBP, which was slightly lower (–2±2 mm Hg) with felodipine than with nifedipine treatment (P<0.05). Secondary: Reported adverse events by patients and providers did not differ between the agents, with the most commonly reported side effect for both groups being leg swelling/edema. There was no difference in use of supplemental antihypertensive agents and heart rate between treatments (P>0.05 for both).
Renal Effects				
Esnault et al.[101] (2008) Amlodipine 5 to 10 mg QD vs enalapril 5 to 20 mg daily	MC, DB, PC, RCT Nondiabetic, adult patients with estimated creatinine clearance of 20 to 60 ml/min	N=263 3 years	Primary: Change in GFR measured yearly by blood clearance Secondary: Composite of renal events and tolerability	Primary: No statistically significant difference was found between amlodipine and enalapril in GFR decline (-4.92 and -3.98 mL/min., respectively, at last observation). Secondary: No statistically significant difference was found between amlodipine and enalapril in the composite secondary end point after a median follow-up of 2.9 years, including in the subgroup of patients with proteinuria >1 g/d at baseline.
Agodoa et al.[72] (2001)	DB, MC, RCT African American	N=1,094 4 years	Primary: Rate of change in GFR (GFR slope)	Primary: The average decline in GFR was slower, by 36% in the ramipril group as compared to the amlodipine group (P=0.002). However, during the first 3-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AASK Amlodipine 5 to 10 mg QD vs ramipril 2.5 to 10 mg QD	patients, age 18 to 70 years old, with hypertensive renal disease (GFR 20 to 65 mL/min)		Secondary: Composite of: confirmed reduction GFR by 50% or by 25 mL/min for baseline, end-stage renal disease	months, GFR increased more in the amlodipine group than the ramipril group (P<0.001). The mean total slope did not differ between the groups (P=0.38). Secondary: The risk reduction for the composite secondary outcome was significantly greater for the ramipril group than the amlodipine group (P=0.005). The rate of end-stage renal disease was significantly lower in the ramipril group (P=0.01).
Wright et al.[74] (2002) AASK Amlodipine 5 to 10 mg QD vs metoprolol 50 to 200 mg QD vs ramipril 2.5 to 10 mg QD	MC, RCT African American patients, age 18 to 70 years old, with hypertensive renal disease (GFR 20 to 65 ml./min)	N=1,094 4 years	Primary: Rate of change in GFR Secondary: Composite of: confirmed reduction in GFR by 50% or by 25 ml/min for baseline, end-stage renal disease, death	Primary: The mean GFR decline did not significantly differ between the usual and lower blood pressure groups for the chronic phase, after 3 months of treatment, or during the 4 year follow-up (P=0.33 and P=0.24). The mean GFR decline was slower in the ramipril treatment group than the in metoprolol group for the acute phase, first 3 months of treatment, and the 4 year follow-up (P=0.01 and P=0.007). The mean GFR decline was faster in the amlodipine treatment group than the in metoprolol group for the chronic phase, but GFR increased during the acute phase, and therefore GFR decline was slower at 3 year follow-up (P=0.02, P<0.001, P=0.004). Secondary: There was no significant difference in the risk of composite secondary outcome between the usual blood pressure group and the lower blood pressure group (P=0.85). There were no significant differences in the risk reduction of composite secondary outcome and end-stage renal disease between the ramipril group and the metoprolol group (P=0.04). There was no difference in the risk of the composite secondary outcome between the amlodipine group and the metoprolol group (P=0.17). The metoprolol group had significantly lower risk than the amlodipine group for end-stage renal disease or death (P=0.003, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lewis et al.[105] (2001) IDNT Amlodipine 10 mg daily vs irbesartan 300 mg daily vs placebo	DB, MC, PC, PRO, RCT Patients 30-70 years old, with type 2 diabetes mellitus, hypertension, and nephropathy	N=1,715 2.6 years	Primary: Composite of risk of doubling serum creatinine, ESRD, or death from any cause Secondary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, heart failure requiring hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation	Primary: Compared to placebo, irbesartan 300 mg daily resulted in a 20% lower relative risk of the composite primary outcome (P=0.02). Irbesartan treatment was associated with a 33% lower risk of doubling serum creatinine (P=0.003) and 23% trend towards lower risk of ESRD (P=0.07) compared to placebo. There was no significant difference in risk of death from any cause for irbesartan compared to placebo (P=0.57). Compared to amlodipine, irbesartan treatment resulted in a 23% lower risk of composite primary outcome (P=0.006). Irbesartan treatment was associated with a 37% lower risk of doubling serum creatinine vs amlodipine (P<0.001) and 23% trend towards lower risk of ESRD vs amlodipine (P=0.07). There was no significant difference in risk of death from any cause (P=0.80). Secondary: There were no significant differences in the secondary cardiovascular composite end point (P=0.40 and P=0.79 for irbesartan vs placebo and amlodipine, respectively). Serum creatinine increased more slowly in the irbesartan group, as compared to the placebo group (24% slower; P=0.008), and the amlodipine group (21% slower; P=0.02).
Viberti et al.[104] (2002) MARVAL Amlodipine 5 mg QD vs valsartan 80 mg QD	AC, DB, RCT Patients 35-75 years old with type 2 diabetes mellitus and microalbuminuria, with or without hypertension	N=332 24 weeks	Primary: Change in UAER; proportion of patients who returned to normal albuminuria Secondary: Proportion of patients returning to normoalbuminuria	Primary: Valsartan resulted in a UAER reduction of 44% at 24 weeks compared to baseline vs an 8% reduction with amlodipine (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive groups. Over the study period, blood pressure reductions were similar between the 2 treatments and at no time point was there a between-group significant difference in blood pressure values in either the hypertensive or the normotensive subgroup. Secondary: The proportion of patients returning to normal albuminuria was greater with valsartan (29.9%) vs amlodipine (14.5%; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bakris et al.[87] (2008) GUARD Amlodipine-benazepril (fixed-dose combination) vs benazepril-HCTZ (fixed-dose combination) Doses were not specified in this reference.	DB, RCT Hypertensive, albuminuric type 2 diabetic patients, mean age 58 years were randomized to receive either initial fixed-dose combination product	N=322 52 weeks	Primary: Change in urinary albumin to creatinine ratio after 1 year of initial treatment with either fixed-dose combination, blood pressure reductions Secondary: Proportion who progressed to overt diabetic nephropathy, safety	Primary: Both combinations significantly reduced the urinary albumin to creatinine ratio compared to baseline (P<0.0001). The median percent change was –72.1% for benazepril/HCTZ and –40.5% for amlodipine/benazepril (P<0.0001). Both regimens significantly reduced SBP and DBP compared to baseline (P<0.0001). The mean reduction in both SBP and DBP was greater in the amlodipine-based arm than in the HCTZ-based arm; however, significance in favor of the amlodipine regimen was observed only for DBP (SBP –20.5 vs –18.8; P=0.19; DPB –13.1 vs –9.97; P=0.02). A greater proportion of patients who had microalbuminuria at baseline and treated with benazepril/HCTZ compared with amlodipine/benazepril attained normalization of the urinary albumin to creatinine ratio, defined as <30 mg/g (69.2% vs 47.8%; P=0.0004). Secondary: The percentage of patients progressing to overt proteinuria was similar for both groups. Overall, both study drugs were well tolerated. Adverse reactions possibly related to the study medications occurred in 11.4% and 3.6% of patients receiving amlodipine/benazepril and benazepril/HCTZ, respectively. They included peripheral edema (7.8% vs 2.4%, respectively), fatigue (1.2% in each group), pitting edema (1.2% vs 0.0%), face edema (0.6% vs 0.0%) and thirst (0.6% vs 0.0%). More patients receiving the HCTZ-based regimen (10.8%) discontinued study drug than with the amlodipine-based regimen due to side effects (5.4%).
Miscellaneous				
Rosendorff et al.[102] (2009) Amlodipine 5 to 10 mg QD vs	DB, AC, RCT Adults with hypertension and left ventricular hypertrophy	N=102 52 weeks	Primary: Change in left ventricular mass from baseline to 52 weeks Secondary:	Primary: Mean ± SD LV masses of 252.9 ± 73.06 g in the olmesartan group and 236.9 ± 59.94 g in the amlodipine group at baseline were decreased to 248.2 ± 69.31 and 223.9 ± 53.18 g, respectively, after 52 weeks of therapy. Neither of these changes was significantly different from baseline, and the difference between the 2 treatment groups was not significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
olmesartan 20 to 40 mg QD			Change in LV mass after 26 weeks of treatment	Secondary: At 26 weeks, adjusted percent changes in LV mass were 8.0% with olmesartan and 6.0% with amlodipine. Changes occurring at the 26-week assessment were not significantly different from baseline or from each other.
Luscher et al.[94] (2009) ENCORE II Nifedipine 30 to 60 mg QD vs placebo	DB, PC, MC, RCT Adults undergoing coronary angiography with or without percutaneous intervention	N=226 18-24 months	Primary: The effect of nifedipine compared with placebo on acetylcholine-induced coronary vascular response at the highest dose of acetylcholine at baseline and follow-up Secondary: Effect of nifedipine on the % change in plaque volume as assessed by intravascular ultrasound	Primary: The change in mean luminal diameter averaged 13.9 ± 16.5% with nifedipine and 7.7 ± 18% with placebo. The difference between groups was 6.3% (95% CI: 1.6-10.9, P=0.0088). Secondary: Neither the difference in absolute nor relative changes in mean plaque volume as measure by intravascular ultrasound between treatments was significant (P=0.84 and 0.66, respectively).
Schmid-Elsaesser et al.[75] (2006) Nimodipine continuous infusion of 1 mg/hour for 6 hours, followed by 2.0 mg/hour	RCT Patients with aneurismal subarachnoid hemorrhage	N=104 7 days	Primary: Incidence of clinical vasospasm and transcranial Doppler angiographic vasospasm, and infarction attributable to vasospasm	Primary: There was no significant difference between the groups in number of patients experiencing clinical vasospasm or transcranial doppler/angiographic vasospasm: 14 patients (27%) in the nimodipine group vs 8 patients (15%) in the magnesium group (P=0.193); 17 (33%) in the nimodipine group vs 20 (38%) in the magnesium group (P=0.792). No difference between the groups was found in incidence of cerebral infarction, 11 (22%) in the nimodipine group vs 10 (19%) in the magnesium group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs magnesium sulfate bolus infusion 10 mg/kg, followed by continuous infusion of 30 mg/kg QD			Secondary: Incidence of angiographic vasospasm	Secondary: There were no significant differences in incidence of angiographic vasospasm, neuronal markers or Glasgow outcome scores (all values: P>0.05).

Drug regimen abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QD=once daily, SR=sustained release
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, XO=crossover
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, DBP=diastolic blood pressure, GFR=glomerular filtration rate, $HbA1_c$=hemoglobin $A1_c$, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

Additional Evidence

Dose Simplification
Taylor et al. evaluated adherence rates in patients receiving a fixed-dose combination of amlodipine/benazepril compared to patients receiving an angiotensin-converting enzyme (ACE) inhibitor and a long-acting dihydropyridine calcium-channel blocking agent as separate formulations.[91] There was no significant difference in adherence in younger subjects (18-39 year olds); however, overall adherence was higher in patients receiving amlodipine/benazepril fixed-dose combination product compared to those receiving separate formulations (80.8% vs 73.8%; P<0.001). Dickson et al. also evaluated adherence rates with the fixed-dose combination of amlodipine/benazepril compared to the administration of an ACE inhibitor and dihydropyridine calcium-channel blocking agent as separate formulations in an elderly Medicaid population.[92] Over a 12 month period, adherence rates were higher in patients receiving the fixed-dose combination product compared to those receiving separate formulations (63.4% vs 49.0%; P<0.0001). Gerbino et al. assessed adherence rates in patients receiving the fixed-dose combination of amlodipine/benazepril or an ACE inhibitor and dihydropyridine calcium-channel blocking agent administered as separate formulations.[96] Adherence rates were 69.2% for patients who received the antihypertensive agents as separate formulations compared to 87.9% for patients receiving the fixed-dose combination product (P<0.0001).

Stable Therapy
Lenz et al. compared the 24-hour blood pressure control in patients stabilized on amlodipine who were then converted to nisoldipine.[52] After 3 months, blood pressure control was similar between treatments, except for average 24-hour diastolic blood pressure, where nisoldipine treatment resulted in slightly greater readings (by 2 mm Hg). Gustin et al. reviewed medical records of hypertensive patients who were switched from long-acting nifedipine to felodipine.[47] This resulted in slightly lower diastolic blood pressure measurements (78 vs 80 mm Hg; P<0.05). Adverse events and supplemental medication use were similar between the agents. Sapienza et al. measured the impact of converting long-term care patients previously on high dose calcium-channel blocking agents or dual therapy with an ACE inhibitor and calcium-channel blocking agents to the fixed-dose combination of amlodipine/benazepril.[93] There was no significant change in blood pressure following the conversion; however, there was a significant reduction in the number of patients reporting ≥1 drug-related adverse event (22 vs 4; P<0.05).

Impact on Physician Visits
Sheehy et al. conducted a comparative review of patients receiving amlodipine or felodipine. The investigators found an increased number of specialist visits in the amlodipine group (odds ratio, 1.14; 95% CI, 18 to 1.20); however, this same group of patients receiving amlodipine had significantly better compliance and refill rates and fewer medication switches.[42]

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 15. Relative Cost of the Dihydropyridines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amlodipine	tablet	Norvasc®*	$$$	$
Amlodipine and benazepril	capsule	Lotrel®*	$$$-$$$$	$$$
Amlodipine and olmesartan	tablet	Azor®	$$$-$$$$	N/A
Amlodipine and valsartan	tablet	Exforge®	$$$-$$$$	N/A
Amlodipine, valsartan, and hydrochlorothiazide	tablet	Exforge HCT®	$$$-$$$$	N/A
Felodipine	extended-release tablet	N/A	N/A	$$-$$$
Isradipine	capsule*, extended-release tablet	DynaCirc CR®	$$$-$$$$	$$$
Nicardipine	capsule, injection, sustained-release capsule	Cardene IV®*, Cardene SR®	$$$	$
Nifedipine	capsule, extended-release tablet	Adalat CC®*, Procardia®*, Procardia XL®*	$$$-$$$$	$$-$$$$
Nimodipine	capsule	Nimotop®*	$$$$$	$$$$$
Nisoldipine	extended-release tablet*	Sular®	$$$-$$$$	$$$-$$$$

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

X. Conclusions

All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension.[1-16] Amlodipine, nicardipine and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented coronary artery disease.[4] Amlodipine is available in combination with benazepril, olmesartan, valsartan, or valsartan/hydrochlorothiazide. It should be noted that the amlodipine/telmisartan fixed-dose combination product is included in the angiotensin II receptor antagonists class review (AHFS Class 243208). All of the single entity dihydropyridines and amlodipine/benazepril are available in a generic formulation.

There are several national and international guidelines that provide recommendations regarding the use of calcium-channel blocking agents (CCBs).[22-28,30-37,39-40] For the treatment of chronic stable angina, β-blockers are recommended as initial therapy; however, CCBs may be used if β-blockers are contraindicated or if additional therapy is required.[22-26] CCBs are recommended as initial therapy in patients with variant/vasospastic angina.[22,24-25] For the treatment of heart failure, ACE inhibitors, angiotensin II receptor antagonists, aldosterone antagonists and isosorbide dinitrate/hydralazine are recommended as initial therapy.[27-29] Amlodipine or felodipine may be added if patients have angina or uncontrolled blood pressure.[27-28] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[30-31,33,37] According to the European

Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, CCBs, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[32,34] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[32,34] The guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[30-37]

Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents.[43-53,55-59,76-90,95,99-100,103,107-113] In studies comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less-intensive treatment regimens.[56,76,79-85,95,99-100,107-112] Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.[46-48,50] Most patients will require more than one antihypertensive agent to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[32,34,91-92,96] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations. The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with β-blockers, diuretics, ACE inhibitors and angiotensin II receptor antagonists.[54-56,60,63-67,69,71,97]

There is insufficient evidence to support that one brand dihydropyridine 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 dihydropyridines 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 dihydropyridine 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 Calcium-Channel Blocking Agents, Miscellaneous
AHFS Class 242892
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I. Overview

The movement of calcium ions is essential for the function of all types of muscle, including cardiac and vascular smooth muscle. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue.[1-3,14] Relaxation of coronary vascular smooth muscle increases the flow of oxygenated blood into the myocardium, while relaxation of arteriolar smooth muscle decreases peripheral vascular resistance.[15-18] Both coronary and systemic vasodilation serve to reduce cardiac workload.[19] The calcium-channel blocking agents include dihydropyridines and miscellaneous agents (nondihydropyridines). Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The nondihydropyridines also block the T-type calcium channel in the atrioventricular node.

The miscellaneous calcium-channel blocking agents include diltiazem and verapamil, which are approved for the treatment of angina, arrhythmias and hypertension.[1-13] Diltiazem is a potent coronary vasodilator, but is only a mild arterial vasodilator. Although it decreases atrioventricular (AV) node conduction, diltiazem does not have negative inotropic properties. Verapamil dilates coronary and peripheral arteries.[8-13] It also slows conduction through the AV node, and has negative inotropic and chronotropic effects. Both diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.

The miscellaneous calcium-channel blocking agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Diltiazem and verapamil are available in a generic formulation. This class was last reviewed in September 2008.

Table 1. Calcium-Channel Blocking Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Diltiazem	extended-release capsule, extended-release tablet, injection, sustained-release capsule, tablet	Cardizem®*, Cardizem CD®*, Cardizem LA®*, Dilacor XR®*, Tiazac®*	diltiazem
Verapamil	extended-release capsule, extended-release tablet, injection, tablet	Calan®*, Calan SR®*, Covera-HS®, Isoptin SR®*, Verelan®*, Verelan PM®*	verapamil

*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 miscellaneous calcium-channel blocking agents are summarized in Table 2. For a comprehensive overview of the pharmacologic management of acute myocardial infarction, angina pectoris, heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Calcium-Channel Blocking Agents, Miscellaneous

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-**	Prophylactic Therapies in the Acute Phase • There is no case for using calcium-channel blocking agents for prophylactic purposes in the acute phase of an MI. • At discharge and in the absence of contraindications, all patients

Clinical Guideline	Recommendation(s)
segment Elevation[37] **(2008)**	should be treated with ASA, a thienopyridine, a β-blocker and a statin. In patients with significant LV dysfunction, an ACE inhibitor (or an ARB) should be added. With the exception of the thienopyridine, these medications should be given indefinitely. Secondary Prevention • The use of verapamil and diltiazem may be appropriate when β-blockers are contraindicated, especially in obstructive airways disease.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI)**[35] **(2007)**	• No specific recommendation is made concerning the miscellaneous calcium-channel blocking agents.
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction**[36] **(2007)**	Secondary Prevention • Calcium-channel blocking agents should not routinely be used to reduce cardiovascular risk after an MI. • Verapamil or diltiazem may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers must be discontinued or in whom β-blockers are contraindicated. • For patients who are stable after an MI, calcium-channel blockers may be used to treat hypertension and/or angina. • For patients with heart failure, amlodipine should be used, and verapamil, diltiazem and short-acting dihydropyridine agents should be avoided.
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**[20] **(2007)**	• Long-acting calcium-channel blocking agents (CCBs) or long-acting nitrates may be used if β-adrenergic blocking agents, (β-blockers) are contraindicated. • Long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris**[19] **(2006)**	Pharmacologic Therapy to Improve Prognosis • CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction (MI) and who do not have heart failure. Symptomatic Treatment and Treatment of Ischemia • If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate. Sinus node inhibition may be considered. Treatment of Syndrome X • Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination. Treatment of Vasospastic/Variant Angina • Treatment with CCBs is recommended. Nitrates may also be used if needed.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary**	Symptomatic Patients • The following agents are recommended to reduce symptoms only: nitroglycerine (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when

Clinical Guideline	Recommendation(s)
Artery Disease[23] (2004)	monotherapy has been unsuccessful.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[21] (2007)**	Early Hospital Care • In patients with continuing or frequently recurring ischemia and in whom β-blockers are contraindicated, a nondihydropyridine calcium-channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction or other contraindications. • Oral long-acting nondihydropyridine calcium-channel blockers are reasonable for use in patients for recurrent ischemia in the absence of contraindications after β-blockers and nitrates have been fully used. • The use of extended-release forms of nondihydropyridine calcium-channel blockers instead of a β-blocker may be considered in patients with UA/NSTEMI. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge • CCBs are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated. Variant (Prinzmetal's) Angina • Treatment with nitrates and CCBs is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions. Cardiovascular "Syndrome X" • Nitrates, β-blockers, and calcium-channel blockers (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)[22] (2007)**	Acute Treatment • CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. • Nondihydropyridine CCBs should not be used unless combined with β-blockers.
American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC): **Guidelines for Management of Patients with Atrial Fibrillation[54] (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

Clinical Guideline	Recommendation(s)
	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. • 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. • When the ventricular rate cannot be adequately controlled both at rest 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. • 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. • 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>Cardioversion of Atrial Fibrillation</u> • 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.
National Institute for Health and Clinical Excellence (NICE): **Atrial Fibrillation**[55] **(2006)**	• β-blockers or rate-limiting calcium antagonists are the recommended first-line agents for rate control in those patients with permanent atrial fibrillation. • 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.
American College of Chest Physicians (ACCP): **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery**[56] **(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.
American Academy of Family Physicians (AAFP)/American	• The recommendations provided in this guideline do not apply to the following patients: those with postoperative or post–MI atrial

Clinical Guideline	Recommendation(s)
College of Physicians (ACP): **Management of Newly Detected Atrial Fibrillation**[57] **(2003)**	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.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline**[25] **(2010)**	Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • CCBs should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. Patients With Heart Failure and Coronary Artery Disease (CAD) • CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**[24] **(2009)**	Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed Heart Failure Symptoms (Stage B) • CCBs with negative inotropic effects are not recommended in asymptomatic patients with low ejection fraction after an MI. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Drugs known to adversely affect patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction (nonsteroidal anti-inflammatory drugs (NSAIDs), some CCBs, some antiarrhythmic medications) should be discontinued and avoided if possible. • CCBs are not recommended as routine treatment for heart failure. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-blockers, ARBs, ACE inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[26] **(2008)**	Management of Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (HFPEF) • No treatment has been shown to reduce morbidity and mortality in patients with HFPEF. • Verapamil may improve exercise capacity and symptoms in these patients. Arrhythmias in Chronic Heart Failure • In patients with heart failure and preserved LVEF, a nondihydropyridine calcium-channel antagonist (alone or in combination with digoxin) should be considered to control the heart rate at rest and during exercise.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management**[53] **(2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction.

Clinical Guideline	Recommendation(s)
	• Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • Several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an ARB or a CCB, and in recent large-scale trials for the ACE inhibitor/CCB combination. The ARB/CCB combination also appears to be rational and effective. These combinations can be recommended for priority use. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[29] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension:**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was

Clinical Guideline	Recommendation(s)
Management in Adults in Primary Care: Pharmacological Update[30] (2006)	with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider a fourth medication or consult a specialist.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[27] (2004)**	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting CCBs may also be used. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease (CVD) and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2 to 4 times higher in African American patients. • CCBs may be useful in Raynaud's syndrome and certain arrhythmias.ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[34] (2004)**	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.

Clinical Guideline	Recommendation(s)
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension[28] (2003)**	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans[33] (2003)**	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[32] (2010)**	• Multiple drug therapy is generally required to achieve blood pressure goals. • During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they can cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous calcium-channel blocking 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 Calcium-Channel Blocking Agents, Miscellaneous[1-13]

Indication	Diltiazem ER	Diltiazem IR	Diltiazem SR	Verapamil ER	Verapamil IR	Verapamil SR
Angina Pectoris						
Treatment of chronic stable angina	✔	✔	✔	✔ †	✔	
Treatment of vasospastic (Prinzmetal's variant) angina	✔	✔	✔		✔	
Treatment of unstable angina					✔	
Arrhythmias						
In association with digitalis for the control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation					✔	
Prophylaxis of repetitive paroxysmal supraventricular tachycardia					✔	
Hypertension						
Treatment of hypertension	✔ *		✔ *	✔	✔	✔

ER=extended-release (24 hour formulations), IR=immediate-release, SR=sustained-release (12 hour formulations)
*Alone or in combination with other antihypertensive agents.
†Covera-HS®

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous calcium-channel blocking agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Calcium-Channel Blocking Agents, Miscellaneous[1-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Diltiazem	35-40	77-93	Liver, extensive	Renal (35) Feces (60-65)	3-10
Verapamil IR	20-35	88-94	Liver (65-80)	Renal (70) Feces (9-16)	4-12

IR=immediate-release

V. Drug Interactions

Significant drug interactions with the miscellaneous calcium-channel blocking agents are listed in Table 5.

Table 5. Significant Drug Interactions with the Calcium-Channel Blocking Agents, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Diltiazem	1	Colchicine	Plasma concentrations of colchicine may be increased by diltiazem. Colchicine toxicity may occur. Inhibition of cytochrome P450 3A4 and/or efflux transporter P-glycoprotein diltiazem may increase the absorption and decrease the metabolic elimination of colchicine.
Diltiazem	1	Macrolides	Increased serum levels of macrolide antibiotics may result if administered with diltiazem, due to diltiazem's inhibitory effect on CYP 3A4. Coadministration should be avoided.
Diltiazem	1	Narcotic Analgesics	Diltiazem may increase plasma concentrations of narcotic analgesics, increasing the potential for enhanced pharmacologic effects and toxicity. Inhibition of cytochrome P450 3A4 isoenzyme by diltiazem may decrease the metabolic elimination of narcotic analgesics.
Diltiazem	1	Statins	Plasma concentrations and pharmacologic effects of statins may be increased by co-administration of diltiazem. The risk of myopathy and rhabdomyolysis may be increased. Inhibition of cytochrome P450 3A4

Generic Name(s)	Significance Level	Interaction	Mechanism
			isoenzymes by diltiazem may decrease the metabolic elimination of statins.
Verapamil	1	β-Blockers	Effects of β-blockers and diltiazem may be increased, close monitoring of cardiac function is recommended. Diltiazem may inhibit the metabolism of some β-blockers (atenolol, metoprolol and propranolol), leading to increased effects of these β-blockers.
Verapamil	1	Colchicine	Plasma concentrations of colchicine may be increased by verapamil. Colchicine toxicity may occur. Inhibition of cytochrome P450 3A4 and/or efflux transporter P-glycoprotein verapamil may increase the absorption and decrease the metabolic elimination of colchicine.
Verapamil	1	Dofetilide	Increase serum levels and effects of dofetilide may occur if coadministered with verapamil, increasing the risk of arrhythmia.
Verapamil	1	Erythromycin	Plasma concentration of erythromycin may be increased by concurrent use of verapamil. Concurrent use should be avoided because elevated concentrations of erythromycin have been associated with an increased risk for sudden death from cardiac causes. Inhibition of cytochrome P450 3A4 isoenzymes by verapamil may decrease the metabolic elimination of erythromycin. Elevated concentrations of erythromycin have been associated with prolongation of the QT interval, torsades de pointes, and an increased risk of sudden death.
Verapamil	1	Macrolides & Ketolides	Increased verapamil serum levels and effects may occur if coadministered, due to inhibition of verapamil metabolism by macrolide antibiotics.
Verapamil	1	Narcotic Analgesics	Verapamil may increase plasma concentrations of narcotic analgesics, increasing the potential for enhanced

Generic Name(s)	Significance Level	Interaction	Mechanism
			pharmacologic effects and toxicity. Inhibition of cytochrome P450 3A4 isoenzyme by verapamil may decrease the metabolic elimination of narcotic analgesics.
Diltiazem	2	Benzodiazepines	Increased serum levels of benzodiazepines may result if administered with diltiazem, increasing the risk of CNS depression, due to decreased metabolism of benzodiazepines.
Diltiazem	2	β-Blockers	Increased serum levels of β-blockers may result if administered with diltiazem, increasing the risk of symptomatic bradycardia, due to decreased metabolism of β-blockers and additive pharmacologic effects.
Diltiazem	2	Carbamazepine	Increased serum levels of carbamazepine may result if administered with diltiazem, increasing the risk of greater effect and toxicity, due to inhibition of carbamazepine metabolism by diltiazem.
Diltiazem	2	Cilostazol	Pharmacologic effects of cilostazol may be increased by diltiazem. Elevated plasma concentrations with toxicity may occur. Inhibition of cytochrome P450 3A4 isoenzymes by diltiazem may decrease the metabolic elimination of cilostazol.
Diltiazem	2	Corticosteroids	Diltiazem may increase the pharmacologic effects of corticosteroids. Inhibition of cytochrome P450 3A4 isoenzymes by diltiazem may decrease the metabolic elimination of corticosteroids.
Diltiazem	2	Cyclosporine	Increased serum levels of cyclosporine may result if administered with diltiazem, due to inhibition of cyclosporine metabolism by diltiazem.
Diltiazem	2	Digoxin	Increased serum levels of digoxin may result, increasing the risk of digoxin toxicity, if administered with diltiazem, due to decreased renal clearance of digoxin.
Diltiazem	2	Everolimus	Pharmacologic effects and

Generic Name(s)	Significance Level	Interaction	Mechanism
			plasma concentrations of everolimus may be increased by diltiazem. Inhibition of CYP3A4 and P-glycoprotein by diltiazem may decrease the metabolic elimination of everolimus.
Diltiazem	2	HIV Protease Inhibitors	Plasma concentrations and pharmacologic effects of diltiazem may be increased by HIV protease inhibitors. An additive effect on the PR interval has also been demonstrated. Plasma concentrations and pharmacologic effects of diltiazem may be increased by HIV protease inhibitors.
Diltiazem	2	Macrolide Immunosuppressives	Plasma trough concentrations of macrolide immunosuppressives may be increased by diltiazem. Neurologic toxicity may occur. Diltiazem may increase the plasma trough concentrations of macrolide immunosuppressives. Neurologic toxicity may occur.
Diltiazem	2	Ranolazine	Increased serum levels of ranolazine may result if administered with diltiazem, due to diltiazem's inhibitory effect on CYP 3A4. Coadministration should be avoided due to the increased risk of QTc prolongation, torsades de pointes arrhythmias and death.
Diltiazem	2	Vasopressin Receptor Antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by diltiazem. Inhibition of CYP 3A isoenzymes by diltiazem may decrease the metabolic elimination of vasopressin receptor antagonists.
Verapamil	2	Aldosterone Blockers	Verapamil may increase plasma concentrations and pharmacologic or toxic effects of aldosterone blockers. Inhibition of cytochrome P450 3A4 isoenzymes by verapamil may decrease the metabolic elimination of aldosterone blockers.
Verapamil	2	Carbamazepine	Increased serum levels of carbamazepine may result if administered with verapamil, increasing the risk of greater effect and toxicity, due to

Generic Name(s)	Significance Level	Interaction	Mechanism
			inhibition of carbamazepine metabolism by verapamil. Close monitoring of carbamazepine levels is recommended and dose alterations may be required if verapamil is discontinued.
Verapamil	2	Clonidine	Sinus bradycardia, AV block and severe hypotension may occur with coadministration of clonidine and verapamil.
Verapamil	2	Cyclosporine	Increased serum levels of cyclosporine may result if administered with verapamil, increasing the risk of nephrotoxicity, due to verapamil's inhibitory effect on cyclosporine metabolism. Close monitoring is recommended and dose adjustments may be required.
Verapamil	2	Digitoxin	Pharmacologic effects of digitoxin may be increased. The extrarenal clearance of digitoxin may be decreased by verapamil.
Verapamil	2	Digoxin	Verapamil may alter the pharmacokinetics and increase serum concentrations of digoxin. Verapamil may decrease nonrenal and total digoxin clearance.
Verapamil	2	Dronedarone	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.
Verapamil	2	Everolimus	Pharmacologic effects and plasma concentrations of everolimus may be increased by verapamil. Inhibition of CYP3A4 and P-glycoprotein by verapamil may decrease the metabolic elimination of everolimus.
Verapamil	2	Flecainide	Increased risk of cardiotoxic effects may occur when flecainide and verapamil are coadministered. Cardiogenic shock or asystole may develop. Pharmacologic effects may be additive or synergistic.

Generic Name(s)	Significance Level	Interaction	Mechanism
Verapamil	2	HMG-CoA reductase inhibitors	Increased serum levels of HMG-CoA reductase inhibitors may result, increasing the risk of toxicities, such as myositis and rhabdomyolysis, if coadministered with verapamil, due to decreased metabolism of HMG-CoA reductase inhibitors.
Verapamil	2	Nondepolarizing muscle relaxants	Increased serum levels of nondepolarizing muscle relaxants may result, increasing the risk of respiratory depression, if coadministered with verapamil, due to calcium's role on muscle contraction.
Verapamil	2	Quinazolines	The combination of verapamil and quinazolines may produce an acute hypotensive effect which is greater than when either drug is taken alone. Verapamil may decrease the first-pass hepatic metabolism and increase the bioavailability of quinazolines.
Verapamil	2	Quinidine	Pharmacologic effects of quinidine may be increased. This combination may produce marked hypotension. Verapamil inhibits the hepatic metabolism of quinidine.
Verapamil	2	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased by co-administration of verapamil. Inhibition of cytochrome P450 3A4 by verapamil may decrease the metabolic elimination of ranolazine.
Verapamil	2	Rifampin	Decreased serum levels of verapamil may result if coadministered with rifampin, due to increased metabolism of verapamil.
Verapamil	2	Vasopressin Receptor Antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by verapamil. Inhibition of CYP3A isoenzymes by verapamil may decrease the metabolic elimination of vasopressin receptor antagonists.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous calcium-channel blocking agents are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Calcium-Channel Blocking Agents, Miscellaneous[1-13]

Adverse Events	Diltiazem	Verapamil
Cardiovascular		
Angina	-	<1
Arrhythmia	<2	-
Atrial fibrillation	-	✔
Atrioventricular dissociation	-	<1
Atrioventricular block	2-8	1-2
Bradycardia	2-6	1
Bundle branch block	<2	-
Chest pain	-	<1
Claudication	-	<1
Congestive heart failure	<2	2
Edema	2-15	-
Extrasystoles	2	-
Flushing	1-2	1
Hypotension	<4	3
Myocardial infarction	-	<1
Palpitations	1-2	<1
Peripheral edema	2-8	2-4
Postural hypotension	-	<1
Syncope	<2	<1
Tachycardia	<2	-
Vasodilation	2-3	-
Ventricular fibrillation	-	✔
Central Nervous System		
Cerebrovascular accident	-	<1
Confusion	-	<1
Depression	<2	-
Dizziness	3-10	1-5
Fatigue	-	2-5
Headache	5-12	1-12
Insomnia	-	<1
Lethargy	-	3
Nervousness	2	-
Paresthesia	-	1
Psychotic symptoms	-	<1
Sleep disturbance	-	1
Somnolence	-	<1
Tremor	<2	<1
Vertigo	-	<1
Dermatologic		
Alopecia	-	<1
Ecchymosis	-	<1
Erythema multiforme	-	<1
Hair color change	-	✔
Hyperhidrosis	-	<1
Hyperkeratosis	-	<1
Petechiae	<2	-
Photosensitivity	<2	-

Adverse Events	Diltiazem	Verapamil
Rash	1-4	1-2
Stevens-Johnson syndrome	<2	-
Toxic epidermal necrolysis	<2	-
Endocrine and Metabolic		
Gout	1-2	-
Gynecomastia	-	<1
Hyperprolactinemia/galactorrhea	-	<1
Gastrointestinal		
Abdominal discomfort	-	<1
Constipation	<4	7-12
Diarrhea	1-2	2
Dry mouth	-	<1
Dysgeusia	<2	-
Dyspepsia	1-6	3
Gingival hyperplasia	<2	<19
Nausea	-	1-3
Vomiting	2	-
Genitourinary		
Acute renal failure	-	✔
Albuminuria	-	-
Crystalluria	-	-
Impotence	-	<1
Nocturia	-	-
Polyuria	-	<1
Sexual dysfunction	-	-
Spotty menstruation	-	<1
Hematological		
Hemolytic anemia	<2	-
Purpura	-	<1
Thrombocytopenia	<2	-
Laboratory Test Abnormalities		
Alkaline phosphatase increase	<2	-
ALT increased	<2	-
AST increased	<2	-
Liver enzyme elevations	-	1
Musculoskeletal		
Arthralgia	-	<1
Extrapyramidal symptoms	<2	-
Muscle cramps	-	<1
Myalgia	2	1
Pain	6	2
Paresthesia	-	1
Weakness	1-4	-
Respiratory		
Bronchitis	1-4	-
Cough	≤3	✔
Dyspnea	1-6	1
Pharyngitis	2-6	-
Rhinitis	<10	-
Sinus congestion	1-2	-
Other		
Abnormal visual accommodation	-	<1
Allergic reaction	<2	-
Amblyopia	<2	-

Adverse Events	Diltiazem	Verapamil
Amnesia	<2	-
Blurred vision	-	<1
Flu-like syndrome	-	4
Parkinsonian syndrome	-	✔
Tinnitus	-	<1

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous calcium-channel blocking agents are listed in Table 7.

Table 7. Usual Dosing Regimens for the Calcium-Channel Blocking Agents, Miscellaneous[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Diltiazem	Chronic Stable Angina: Tablet (IR): initial, 30 mg four times a day; maintenance, 180 to 360 mg daily Capsule (ER): initial, 120 mg; maintenance, 180 to 480 mg daily; maximum, 480 mg daily Hypertension: Capsule (SR): initial, 60 to 120 mg twice daily; maintenance, 240 to 360 mg daily Capsule (ER): initial, 180 to 240 mg once daily; maintenance, 180 to 480 mg daily; maximum, 540 mg daily Vasospastic Angina: Tablet (IR): initial, 30 mg four times a day; maintenance, 180 to 360 mg daily	Safety and efficacy in children have not been established.	Capsule (ER): 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg Capsule (SR): 60 mg 90 mg 120 mg Injection: 5 mg/ml 100 mg Tablet (ER): 120 mg 180 mg 240 mg 300 mg 360 mg 420 mg Tablet (IR): 30 mg 60 mg 90 mg 120 mg
Verapamil	Arrhythmias: Tablet (IR): 240 to 320 mg three to four times daily Chronic Stable Angina: Tablet (IR): 80 to 120 mg three times a day Tablet (ER): 180 to 480 mg daily at bedtime	Safety and efficacy in children have not been established.	Injection: 2.5 mg/ml Capsule (ER): 100 mg 120 mg 180 mg 200 mg 240 mg 300 mg 360 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Hypertension: Tablet (IR): initial, 80 mg three times a day; maintenance, 360 to 480 mg daily divided (three to four times daily); maximum, 480 mg daily Tablet (ER): 180 to 480 mg daily Tablet (SR): 180 mg once daily in the morning; may titrate up at weekly intervals to 240 mg every 12 hours Paroxysmal Supraventricular Tachycardia: Tablet (IR): 240-320 mg daily in 3 to 4 divided doses Unstable Angina: Tablet (IR): 80 to 120 mg three times a day Vasospastic Angina: Tablet (IR): 80 mg to 120 mg three times daily		Tablet (ER): 120 mg 180 mg 240 mg Tablet (IR): 40 mg 80 mg 120 mg

ER=extended-release, IR=immediate-release, SR=sustained-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous calcium-channel blocking agents are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Calcium-Channel Blocking Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Angina				
De Rosa et al.[38] (1998) Diltiazem SR 300 mg QD vs verapamil SR 240 mg QD	DB, XO Men and women, age 48 to 72 years, with stable exertional angina, a positive test for myocardial ischemia and documented coronary artery disease	N=20 12 weeks	Primary: Exercise tolerance test: time to onset of angina, time to 1-mm ST-segment depression and total exercise duration Secondary: Heart rate, angina frequency, nitroglycerin use and adverse events	Primary: Time to onset of angina increased significantly in both groups compared to placebo (verapamil vs placebo; P<0.05 and diltiazem vs placebo; P<0.005). Time to 1-mm ST-segment depression increased significantly in both groups compared to placebo (verapamil vs placebo; P<0.05 and diltiazem vs placebo; P<0.005). Total exercise duration increased significantly in both groups compared to placebo (verapamil vs placebo; P<0.05 and diltiazem vs placebo; P<0.005). For each primary endpoint, there was no significant difference between the treatment groups. Secondary: Heart rates were similar between the treatment groups, except resting heart rate was significantly lower in the diltiazem group as compared to the verapamil group (68.5 vs 75.9; P<0.05). Angina frequency and nitroglycerin use decreased significantly in the diltiazem group compared to placebo (P<0.05) and to verapamil (P<0.05). Edema and flushing were most frequently reported. Similar rates of adverse events were reported for both treatments.
Chugh et al.[39] (2001) Diltiazem 240 mg QD for 2 weeks	DB, DD, PG, RCT Patients with stable angina, blood pressure in the	N=67 4 weeks	Primary: Treadmill exercise test: time to onset of angina, time to 1-mm ST-segment	Primary: Both treatment groups, and all doses, had significant increases in time to onset of angina from baseline (P<0.001 for all). There was no significant difference between the treatment groups (P=0.838) and between dose levels (P=0.144) in time to onset of angina.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
then 360 mg QD for 2 weeks vs amlodipine 5 mg QD for 2 weeks then 10 mg QD for 2 weeks	range of 100/60 mm Hg to 170/110 mm Hg and a positive ischemic response on a treadmill test, history of angiography		depression Secondary: Heart rate, blood pressure, number of angina episodes and use of nitrates	Both treatment groups, and all doses, had significant increases in time to 1-mm ST-segment depression from baseline, except low-dose amlodipine (P<0.004, except P=0.063). There was no significant difference between the treatment groups and between dose levels (P=0.114) in time to 1-mm ST-segment depression (P=0.691). Secondary: There was no significant difference between the groups in heart rate at rest or maximal exercise. There was no significant difference between the groups in blood pressure at rest or maximal exercise, except SBP at rest was higher in the diltiazem group (137 to 143 vs 129 to 135 mm Hg; P=0.029). Both treatments reduced the number of angina episodes and the use of nitrates, but there was no significant difference between the groups.
van Kesteren et al.[40] (1998) Diltiazem CR 90 to 120 mg BID vs amlodipine 5 to 10 mg QD	DB, MC Men and women, age 41 to 77 years, with a history of stable angina pectoris, a positive exercise tolerance test, and positive thallium scan or positive coronary angiogram	N=132 8 weeks	Primary: Exercise tolerance test: time to 1-mm ST-segment depression, time to onset of chest pain, time to end of exercise (exercise duration) Secondary: Safety	Primary: Diltiazem and amlodipine treatment resulted in significant increases in time to 1-mm ST-segment depression as compared to baseline (P<0.0001). Treatments were not significantly different from each other (P>0.05). Diltiazem and amlodipine treatment resulted in significant increases in time to onset of chest pain at 4 and 8 weeks, (10% and 13% for amlodipine; P<0.0001; 5% and 7% for diltiazem; P=0.009). Treatments were not significantly different from each other (P>0.05). Amlodipine treatment resulted in a significant increase in total exercise duration as compared to baseline (P=0.0002), however the change from baseline for diltiazem was not significantly increased (P=0.43). There was no significant difference between the treatment groups at endpoint. Secondary: 10 patients (15.2%) in the amlodipine group and 17 patients (25.8%) in the diltiazem group reported an adverse event; 2 patients from the amlodipine group and 6 patients from the diltiazem group subsequently withdrew from the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Frishman et al.[41] (1999) Diltiazem 240 to 480 mg at bedtime vs amlodipine 5 to 10 mg QD vs amlodipine 5 to 10 mg QD plus atenolol 50 mg QD vs placebo	DB, MC, PC, PG, RCT Patients, age 30 to 80 years, with chronic stable angina pectoris, evidence of exercise-induced ST-segment depression ≥1 mm and other evidence of cardiac disease	N=551 4 week	Primary: Exercise tolerance test (symptom-limited exercise duration, time ≥1-mm ST-segment depression and time to moderate angina) Secondary: 48-hour Holter-determined number of ischemic episodes, mean and total duration of ischemia, maximal depth of ST depression, heart rate at onset of ischemia	Primary: Treatment with diltiazem, amlodipine, amlodipine plus atenolol resulted in significantly better results than placebo in: symptom-limited exercise duration, time ≥1-mm ST-segment depression and time to moderate angina (P≤0.01 for all vs placebo). Secondary: Treatment with diltiazem, amlodipine, amlodipine and atenolol resulted in significantly fewer ischemic episodes in 48-hour Holter monitoring (P=0.003 for verapamil vs placebo). Treatment with amlodipine monotherapy resulted in a significant increase in duration of ischemic episode (P≤0.05 vs verapamil vs amlodipine plus atenolol and vs placebo). Treatment with verapamil and with amlodipine plus atenolol resulted in a decrease in duration of ischemic episodes as compared to amlodipine and placebo (P≤0.05 for each). HR at the onset of ischemic episode was significantly lower in the verapamil group and in the amlodipine plus atenolol group (P≤0.05 vs amlodipine) and higher in the amlodipine group (P≤0.05 vs verapamil, vs amlodipine plus atenolol and vs placebo).
Hypertension				
Wright et al.[42] (2004) Diltiazem graded-release 360 to 540 mg QD vs amlodipine 5 to 10 mg QD	AC, DB, MC, PG, RCT Male and female African Americans, age 18 to 80 years, with hypertension: DBP 85 to 109 mm Hg and SBP <180 mm Hg	N=268 12 weeks	Primary: Change from baseline in DBP during first 4 hours of awakening as recorded by ambulatory blood pressure monitoring Secondary: Changes from baseline in blood	Primary: Reductions in DBP during the first 4 hours after awakening, and from 6 AM to noon, were significantly greater in the diltiazem group than in the amlodipine group (–13.12 vs –9.65 mm Hg; P=0.0049 and –11.97 vs –8.75 mm Hg; P=0.0019). Secondary: Reductions in SBP during the first 4 hours after awakening and between 6 AM and noon, were similar between the groups (P<0.0768 and P<0.9470). Mean 24-hour SBP reductions were significantly greater in the amlodipine group than in the diltiazem group (–14.08 vs –10.64; P=0.0022).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			pressure, heart rate, rate-pressure product, safety	Reductions in heart rate were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: –4.88 vs 1.77; P<0.0001). Reductions in rate-pressure product were significantly greater in the diltiazem group than in the amlodipine group (24 hour mean: –1493 vs –881; P<0.0008).
White et al.[43] (2004) Diltiazem ER 240 to 540 mg at bedtime vs ramipril 5 to 20 mg at bedtime	DB, MC, PG, RCT Men and women, with hypertension: DBP 90 to 110 mm Hg	N=261 10 weeks	Primary: Change in early morning DBP from baseline Secondary: Change in SBP from baseline, heart rate, heart rate × systolic blood pressure product, 24-hour ambulatory monitoring, safety	Primary: Changes in early morning DBP were significantly larger in the diltiazem group than in the ramipril group (–15 vs –8 mm Hg; P<0.001). Secondary: Changes in early morning SBP were significantly larger in the diltiazem group than in the ramipril group (–18 vs –13 mm Hg; P=0.002). Decreases in heart rate and heart-rate systolic BP product were significantly larger in the diltiazem group than in the ramipril group (–8.9 vs –2.7 beats/min; P<0.0001 and –2518 vs –1393; P<0.0001). Reductions in DBP and heart rate and increases in the rate-pressure product measured by 24-hour ambulatory monitoring and clinic monitoring were significantly greater for diltiazem than for ramipril (P<0.0001 for all). 50% of diltiazem patients and 40% of ramipril patients reported experiencing any adverse event; edema and cough respectively were most frequently reported for each treatment. Withdrawal rates from the study were low and similar between the groups.
Rosei et al.[44] (1997) VHAS Verapamil SR 240 mg QD vs	DB (1st 6 months), MC, PG, RCT Males and females, age 40 to 65 years, with hypertension: SBP ≥160 mm Hg and DBP ≥95 mm Hg	N=1,414 2 years	Primary: Blood pressure Secondary: Cardiovascular events, adverse events	Primary: Both treatments significantly reduced SBP and DBP compared to baseline, however reductions did not significantly differ between treatments: verapamil reduction of 27.6/17 mm Hg vs chlorthalidone reduction of 28.6/16.6 mm Hg (P<0.01 for each vs baseline). Goal DBP was achieved in 69.3% of patients receiving verapamil and 66.9% of patients receiving chlorthalidone. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
chlorthalidone 25 mg QD				Serum total cholesterol levels and heart rate decreased significantly in the verapamil group as compared to baseline and the chlorthalidone treatment group (total cholesterol; P<0.01 for both: heart rate; P<0.05). The number of nonfatal cardiovascular events was similar between the groups, 37 in the verapamil group and 39 in the chlorthalidone group. The number of cardiovascular deaths was similar between the groups, 5 in the verapamil group and 4 in the chlorthalidone group. Hypokalemia and hyperuricemia occurred significantly more frequently in the chlorthalidone group than in the verapamil group (P<0.01 for both). 236 patients reported 403 adverse events in the chlorthalidone group and 230 patients reported 387 adverse events in the verapamil. Asthenia was the most commonly reported adverse event in the chlorthalidone group and constipation was the most commonly reported adverse event in the verapamil group.
Messerli et al.[45] (2006) Verapamil SR 240 mg QD vs trandolapril 4 mg QD vs verapamil SR 240 mg and trandolapril 4 mg QD (separate entities)	DB, MC, PC, PG, RCT Patients, 21 years old and older with DBP of 95 to 114 mm Hg	N=581 6 weeks	Primary: Blood pressure	Primary: All 3 treatment groups had significant blood pressure reductions from baseline (P<0.01 for all). Patients receiving the combination of trandolapril and verapamil had significantly greater reductions in blood pressure as compared to patients receiving trandolapril or verapamil alone (P<0.01 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Outcomes				
Boden et al.[46] (2002) INTERCEPT Diltiazem 300 mg QD vs placebo	DB, MC, PG, PRO, RCT Patients, age 75 years old and younger, with acute myocardial infarction, without congestive heart failure and who received a thrombolytic agent	N=874 Up to 6 months	Primary: Composite first-event rate of: cardiac death, nonfatal reinfarction or refractory ischemia Secondary: Composite of first occurrence of cardiac death, nonfatal reinfarction, recurrent ischemia, composite of cardiac death, nonfatal reinfarction, need for myocardial revascularization	Primary: There was no significant difference between diltiazem treatment and placebo in composite event rate: 131 primary outcome events occurred in the placebo group and 97 occurred in the diltiazem group (P=0.07). Secondary: Rates of all composite nonfatal cardiac events (nonfatal reinfarction combined with refractory ischemia or all recurrent ischemia or need for revascularization) significantly favored diltiazem over placebo (P=0.05, P=0.05, P=0.03 respectively). Rates of cardiac death, nonfatal reinfarction, refractory ischemia and all recurrent ischemia were similar between the diltiazem group and the placebo group, however the need for revascularization favored the diltiazem group (P=0.67, P=0.47, P=0.07, P=0.07, P=0.03). There was no increase in rates of congestive heart failure, bleeding, cancer or cerebrovascular accidents in the diltiazem group.
Gibson et al.[47] (2000) Diltiazem 60 mg QID or verapamil 120 mg TID vs placebo	RETRO Patients suffering acute non-Q-wave myocardial infarction	N=817 (2 trials) 12-18 months	Primary: All cause mortality Secondary: Combined cardiac events	Primary: Patients receiving treatment (either agent) had a 42% lower mortality rate than those receiving placebo (P=0.010). Secondary: Patients receiving treatment (either agent) had a 31% lower event rate (death or recurrent myocardial infarction) than those receiving placebo (P<0.006).
Hansson et al.[50] (2000) NORDIL	Blinded endpoint, MC, open, PRO, RCT Patients, age 50 to	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 10; 95% CI, 0.87 to 1.15; P=0.97). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Diltiazem 180 to 360 mg QD vs conventional therapy (diuretic, β-blocker or both)	74 years, with DBP ≥100 mm Hg and previously untreated		myocardial infarction, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal myocardial infarction	Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal myocardial infarction occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including: cardiovascular death (P=0.41), all cardiac events (P=0.57 and congestive heart failure (P=0.42).
Pepine et al.[48] (2003) INVEST Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD	MC, OL, RCT Patients, age 50 years old and older, with hypertension, requiring drug therapy (blood pressure>140/90 mm Hg or >130/80 mm Hg if diabetic or with renal impairment), and documented coronary artery disease	N=22,576 24 months	Primary: First occurrence of combined: death (all-cause), nonfatal myocardial infarction, or nonfatal stroke Secondary: Occurrence of: death (all-cause), nonfatal myocardial infarction, nonfatal stroke; time to most serious event, cardiovascular death, angina, cardiovascular hospitalization, blood pressure control, cancer, Alzheimer disease, Parkinson disease, gastrointestinal	Primary: There was no significant difference between the verapamil group and the atenolol group in time to first occurrence of death, nonfatal myocardial infarction and nonfatal stroke (P=0.57). 1,171 events were reported by 1,119 patients in the verapamil group and 1,209 events were reported by 1,150 patients in the atenolol group. Secondary: All cause death occurred in 873 patients in the verapamil group and 893 patients in the atenolol group (P=0.72). Equal number, 431 in each treatment group was classified as cardiovascular. Nonfatal myocardial infarctions were reported in 151 patients in the verapamil group and 153 patients in the atenolol group (P=0.95). Nonfatal strokes were reported in 131 patients in the verapamil group and 148 patients in the atenolol group (P=0.33). There was no significant difference between the verapamil group and the atenolol group in cardiovascular related death or hospitalization (P=0.94, P=0.59). Reported angina decreased similarly in both groups (P=0.18), however the average frequency was lower in the verapamil group as compared to the atenolol group (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			tract bleeding, adverse events	There was no significant difference between the verapamil group and the atenolol group in reduction of SBP (verapamil –18.7 vs –19.0 mm Hg; P=0.41) and DBP (verapamil –10.0 vs –10.2 mm Hg; P=0.26). Overall, 71.7% of verapamil and 70.7% of atenolol patients achieved blood pressure goal at 24 months (P=0.18). The average resting heart rate was lower in the atenolol group than the verapamil group (69.2 beats/minute vs 72.8 beats/minute; P<0.001). Rates did not differ between the groups for rates of cancer, Alzheimer disease, Parkinson disease or gastrointestinal tract bleeding (all P>0.05). Constipation and cough were reported more frequently with verapamil mil and dyspnea, lightheadedness, symptomatic bradycardia and wheezing were more frequently reported in the atenolol group.
Mancia et al.[49] (2007) Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD	MC, OL, RCT Patients with hypertension, requiring drug therapy (blood pressure>140/90 mm Hg or >130/80 mm Hg if diabetic or with renal impairment), and coronary artery disease	N=22,576 24 months	Primary: Occurrence of death, nonfatal myocardial infarction and nonfatal stroke Secondary: Blood pressure control rates	Primary: Rates (death, nonfatal myocardial infarction and nonfatal stroke) were similar for both treatment groups. Secondary: Rates of death, myocardial infarction and stoke declined as the number of office visits for which blood pressure was controlled increased (P<0.001).
Black et al.[51] (2003) CONVINCE Verapamil ER 180 mg QD	AC, DB, MC, RCT Patients, age 55 years and older, with hypertension and at least one risk factor for cardiovascular	N=16,476 3 years	Primary: Composite: first occurrence of acute myocardial infarction, stroke or cardiovascular disease-related death	Primary: There was no significant difference between the verapamil treatment group and the atenolol/HCTZ treatment group in the composite primary endpoint (HR, 12; 95% CI, 0.88 to 1.18; P=0.77). Secondary: There was no significant difference between the verapamil treatment group and the atenolol/HCTZ treatment group in rates of cardiovascular-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atenolol 50 mg QD vs HCTZ 12.5 mg QD	disease		Secondary: Cardiovascular endpoints, all-cause mortality, cancer, hospitalization for bleeding, incidence of primary endpoints between 6 AM and noon, adverse events	related hospitalization (P=0.31) and death (all-cause mortality) (P=0.32), cancer rates (P=0.46). Patients treated with verapamil experience a significantly higher rate of death or bleeding unrelated to stroke (HR, 1.54; 95% CI, 1.15 to 2.04; P=0.003). Primary endpoints did not differ significantly based on time of day (P=0.43). Patients treated with verapamil were more likely to withdraw for adverse events or symptoms than those in the atenolol or HCTZ (P=0.02).
Miscellaneous				
Siu et al.[52] (2009) Diltiazem IV 0.25 mg/kg to 10 mg/kg vs digoxin IV 0.5 mg to 0.25 mg vs amiodarone IV 300 mg to 10 mg/kg	OL, RCT Patients who presented to the ER with symptomatic acute atrial fibrillation for <48 hours and rapid ventricular rate >120 bpm necessitating hospitalization	N=150 3 years	Primary: Sustained ventricular rate control (<bpm) within 24 hours Secondary: Time to ventricular control, atrial fibrillation symptom improvement, hospital stay, and adverse events	Primary: The time to ventricular control for the 45 patients assigned to diltiazem was achieved 90% of the time compared to digoxin (74%) and amiodarone (74%) (P<0.0001). Secondary: The median time to ventricular control was significantly shorter in the diltiazem group (3 hours, 1-21 hours) compared with the digoxin (6 hours, 3-15 hours, P<0.001) and amiodarone groups (7 hours, 1-18 hours, P=0.003). The diltiazem group had the largest reduction in atrial fibrillation frequency score and severity score (P<0.0001). Length of hospital stay was significantly shorter in the diltiazem group (3.9 ± 1.6 days) compared with digoxin (4.7 ± 2.1 days, P+0.023) and amiodarone groups (4.7 ± 2.2 days, P=0.038).

Drug regimen abbreviations: BID=twice daily, CR=controlled release, ER=extended release, QD=once daily, QID-four times daily, SR=sustained release, TID=three times a day
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=risk ratio, XO=crossover
Miscellaneous abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

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 Calcium-Channel Blocking Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Diltiazem	extended-release capsule, extended-release tablet, injection, sustained-release capsule, tablet	Cardizem®*, Cardizem CD®*, Cardizem LA®*, Dilacor XR®*, Tiazac®*	$$$-$$$$$	$-$$$
Verapamil	extended-release capsule, extended-release tablet, injection, tablet	Calan®*, Calan SR®*, Covera-HS®, Isoptin SR®*, Verelan®*, Verelan PM®*	$$$-$$$$	$-$$$

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

X. Conclusions

The miscellaneous calcium-channel blocking agents are approved for the treatment of angina, arrhythmias and hypertension.[1-13] Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action. Both drugs are available in a generic formulation.

There are several national and international guidelines that provide recommendations regarding the use of calcium-channel blocking agents (CCBs). [19-30,32-37,53-57] For the treatment of chronic stable angina, β-blockers are recommended as initial therapy; however, CCBs may be used if β-blockers are contraindicated or if additional therapy is required.[19-23] CCBs are recommended as initial therapy in patients with variant/vasospastic angina.[19,21-22] Verapamil or diltiazem may be considered for secondary prevention of cardiovascular disease in patients without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers are contraindicated.[36-37] Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm.[54] The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies.[54] β-blockers and nondihydropyridine CCBs are recommended for patients with persistent or permanent atrial fibrillation, either alone or in combination with digoxin.[54-55,57] CCBs are not recommended for the routine treatment of heart failure; however, verapamil and diltiazem may be considered in patients with preserved left ventricular ejection fraction who have atrial fibrillation requiring ventricular rate control (with intolerance to β-blockers), angina or hypertension.[24-26] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[27-28,30,34] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, CCBs, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[29,53] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[29,53] Guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[27-30,32-34,53]

Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure.[4-13,38-45] Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo, atenolol and hydrochlorothiazide.[47-51]

There is insufficient evidence to support that one brand miscellaneous calcium-channel blocking agent 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 miscellaneous calcium-channel blocking 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 miscellaneous calcium-channel blocking 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 Angiotensin-Converting Enzyme Inhibitors
AHFS Class 243204
November 10, 2010

I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[21-22] Excessive activity of the RAAS may lead to hypertension, as well as fluid and electrolyte disorders.[23] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase).[21] Angiotensin II can increase blood pressure by direct vasoconstriction, as well as through actions on the brain and autonomic nervous system.[21,23] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental effects, which includes ventricular hypertrophy, remodeling and myocyte apoptosis.[21-22]

The ACE inhibitors are approved for the treatment of diabetic nephropathy, heart failure, hypertension and post-myocardial infarction.[1-20] They block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, which is a potent vasodilator.[24] However, this increase in bradykinin also leads to an increase in adverse effects, including cough. The ACE inhibitors are available as single entity products, as well as in combination with hydrochlorothiazide or verapamil. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node, and has negative inotropic and chronotropic effects.

The angiotensin-converting enzyme inhibitors 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 September 2008.

Table 1. Angiotensin-Converting Enzyme Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Benazepril	tablet	Lotensin®*	benazepril
Benazepril and hydrochlorothiazide	tablet	Lotensin HCT®*	benazepril and hydrochlorothiazide
Captopril	tablet	N/A	captopril
Captopril and hydrochlorothiazide	tablet	N/A	captopril and hydrochlorothiazide
Enalapril	tablet	Vasotec®*	enalapril
Enalapril and hydrochlorothiazide	tablet	Vaseretic®*	enalapril and hydrochlorothiazide
Enalaprilat	injection^	N/A	enalaprilat dihydrate
Fosinopril	tablet	Monopril®*	fosinopril
Fosinopril and hydrochlorothiazide	tablet	N/A	fosinopril and hydrochlorothiazide
Lisinopril	tablet	Prinivil®*, Zestril®*	lisinopril
Lisinopril and hydrochlorothiazide	tablet	Prinzide®*, Zestoretic®*	lisinopril and hydrochlorothiazide
Moexipril	tablet	Univasc®*	moexipril
Moexipril and hydrochlorothiazide	tablet	Uniretic®*	moexipril and hydrochlorothiazide
Perindopril	tablet	Aceon®*	perindopril, Aceon®*
Quinapril	tablet	Accupril®*	quinapril
Quinapril and hydrochlorothiazide	tablet	Accuretic®*	quinapril and hydrochlorothiazide

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ramipril	capsule, tablet	Altace®*	ramipril
Trandolapril	tablet	Mavik®*	trandolapril
Trandolapril and verapamil	extended-release tablet	Tarka®*	trandolapril and verapamil

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
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 angiotensin-converting enzyme inhibitors are summarized in Table 2. For a more comprehensive overview of the pharmacologic treatment of acute myocardial infarction, angina pectoris, heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Angiotensin-Converting Enzyme Inhibitors

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation[42] (2008)**	Prophylactic Therapies in the Acute Phase • An oral ACE inhibitor should be given on the first day in the absence of contraindications in patients with significant LV dysfunction. • At discharge and in the absence of contraindications, all patients should be treated with ASA, a thienopyridine, a β-blocker and a statin. In patients with significant LV dysfunction, an ACE inhibitor (or an ARB) should be added. With the exception of the thienopyridine, these medications should be given indefinitely. Secondary Prevention • ACE inhibitor in all patients without contraindications, regardless of blood pressure or LV function.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI)[40] (2007)**	Initial and Hospital Management • Oxygen, morphine, nitroglycerin (NTG), angiotensin-converting enzyme inhibitors (ACE inhibitors), β-adrenergic blocking agents (β-blockers), and aspirin may be used in patients presenting with an MI. Patients should be considered for reperfusion therapy. Secondary Prevention • For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with β-blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure. • ACE inhibitors should be started and continued indefinitely in all patients recovering from STEMI with LVEF ≤40% and for those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. • ACE inhibitors should be started and continued indefinitely in patients recovering from STEMI who are not lower risk (lower risk defined as those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed), unless contraindicated. • Among lower risk patients recovering from STEMI (i.e., those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed) use of ACE inhibitors is reasonable. • Considering use of angiotensin receptor blockers in combination with ACE inhibitors in systolic dysfunction HF may be reasonable.
National Institute for Health and	Secondary Prevention

Clinical Guideline	Recommendation(s)
Clinical Excellence (NICE): **Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction[41] (2007)**	• All patients who have had an acute MI should be offered treatment with a combination of the following drugs: ACE inhibitor, aspirin, β-blocker, and statin. • ACE inhibitors are recommended early after presentation with an acute MI. • After an MI, all patients with preserved left ventricular function or with left ventricular systolic dysfunction should continue treatment with an ACE inhibitor indefinitely, whether or not they have symptoms of heart failure. • Combination therapy with an ACE inhibitor and an angiotensin receptor blocker is not routinely recommended in patients early after an acute MI with heart failure and/or left ventricular systolic dysfunction.
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[25] (2007)**	• Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including ACE inhibitors and/or β-adrenergic blocking agents (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 mm Hg or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction of ≤40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal left ventricular ejection fraction in whom cardiovascular risk factors remain well controlled and revascularization has been performed) unless contraindicated.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris[27] (2006)**	Pharmacologic Therapy to Improve Prognosis • ACE inhibitors should be considered in patients with stable angina and comorbid hypertension, diabetes, heart failure, asymptomatic left ventricular dysfunction, and patients who have had a myocardial infarction. Patients with stable angina who do not have an indication for an ACE inhibitor may be treated with one if the benefits of the agent (possible absolute risk reduction) outweigh the possible side effects. Treatment of Syndrome X • ACE inhibitors are recommended in patients with hypertension.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease[29] (2004)**	Symptomatic Patients • The following agents are recommended to prevent MI or death and to reduce symptoms: aspirin (clopidogrel may be used in patients intolerant to aspirin), β-blockers, statins, and ACE inhibitors. Asymptomatic Patients With Evidence Suggesting CAD on Previous Testing • The following agents should be used to prevent myocardial infarction and death: aspirin (in patients with a previous myocardial infarction), β-blockers (in patients with a previous myocardial infarction), statins (in patients with type 2 diabetes or documented CAD), and an ACE inhibitor (in patients with documented CAD and diabetes, systolic dysfunction, or both). • The following agents may also be used to prevent myocardial infarction and death: aspirin in patients who have not had a previous myocardial infarction, and an ACE inhibitor in patients with diabetes and no contraindications.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007**	Early Hospital Care • An ACE inhibitor should be administered orally within the first 24 hours to UA/NSTEMI patients with pulmonary congestion or LVEF

Clinical Guideline	Recommendation(s)
Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[26] (2007)	≤40% in the absence of hypotension or contraindications. • An ACE inhibitor administered orally within the first 24 hours of UA/NSTEMI can be useful in patients without pulmonary congestion or LVEF ≤40% in the absence of hypotension or contraindications. • An intravenous ACE inhibitor should not be given to patients within the first 24 h of UA/NSTEMI because of the increased risk of hypotension. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge • ACE inhibitors should be initiated and continued indefinitely in patients with heart failure, left ventricular dysfunction, diabetes, or hypertension unless contraindicated. • ACE inhibitors are reasonable for all patients, even without left ventricular dysfunction, hypertension, or diabetes unless contraindicated. • ACE inhibitors are reasonable for patients with heart failure and left ventricular ejection fraction >40%. • Angiotensin receptor blockers should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and signs of heart failure and left ventricular ejection fraction <40%. • Combination ACE inhibitor and angiotensin receptor blocker therapy may be considered in patients with persistent symptomatic heart failure and left ventricular ejection fraction <40% despite conventional therapy including an ACE inhibitor or angiotensin receptor blocker alone. • In patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with chronic kidney disease or diabetes mellitus), it is useful to add blood pressure medication(s) as tolerated, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve target blood pressure.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)[28] (2007)**	Long-term Management • ACE inhibitors are recommended in all patients with left ventricular ejection fraction ≤40% and in patients with diabetes, chronic kidney disease, and hypertension unless otherwise contraindicated. • ACE inhibitors should be considered for all other patients to prevent the recurrence of ischemia. Agents and doses of proven efficacy are recommended (ramipril and perindopril).
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline[31] (2010)**	Patients With Risk Factors for Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction • ACE inhibitors are recommended for asymptomatic patients with reduced LVEF <40%. • Routine use of the combination of ACE inhibitors and ARBs for prevention of heart failure is not recommended. Patients With Left Ventricular Systolic Dysfunction • ACE inhibitors should be used in symptomatic and asymptomatic patients with a LVEF ≤40%. • The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40% post-MI and non post-MI. • The triple combination of an ACE inhibitor, an ARB, and an

Clinical Guideline	Recommendation(s)
	aldosterone antagonist is not recommended because of the high risk of hyperkalemia. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. Patients With Heart Failure and Coronary Artery Disease (CAD) • ACE inhibitors are recommended in all patients with either reduced or preserved LVEF after an MI. • ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) in stable hospitalized post-MI patients with LVEF or heart failure. Patients With Heart Failure and Hypertension • The use of an ACE inhibitor is recommended. Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended. Managing Heart Failure in Special Populations • Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure and LVEF. • ACE inhibitor and β-blocker therapy are recommended in all women with symptomatic or asymptomatic heart failure and LV systolic dysfunction. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with symptomatic or asymptomatic heart failure and LV systolic dysfunction.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**[30] **(2009)**	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors, and β-blockers have been shown to prevent heart failure. • ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. • ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction, and heart failure. • ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes, and hypertension with other cardiovascular risk factors. Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed Heart Failure Symptoms (Stage B) • β-blockers and ACE inhibitors should be used in all patients with a recent or past history of MI regardless of ejection fraction or presence of heart failure. • β-blockers and ACE inhibitors should be used in patients who have reduced left ventricular ejection fraction and do not have a history of MI or heart failure. • ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • ACE inhibitors are recommended in all patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction

Clinical Guideline	Recommendation(s)
	unless contraindicated. • The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-Blockers, ARBs, ACE inhibitors, and calcium-channel blocking agents may be useful in patients with heart failure and controlled hypertension to improve symptoms. Hospitalized Patients • Oral therapies known to improve outcomes (ACE inhibitors, angiotensin receptor blockers, β-blockers) should be continued during hospitalization. If not currently treated with these therapies, initiation is recommended prior to hospital discharge.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[32] **(2008)**	Pharmacologic Therapy of Chronic Heart Failure • ACE inhibitors are recommended in patients with LVEF ≤40% irrespective of symptoms. Comorbidities and Special Populations • Antihypertensive regimens based on renin–angiotensin system antagonists (ACE inhibitors or ARBs) are preferable. • In hypertensive patients with HFPEF, aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended. ACE inhibitors and/or ARBs should be considered the first-line agents. • ACE inhibitors and ARBs can be useful in patients with diabetes mellitus to decrease the risk of end-organ damage and cardiovascular complications and subsequently risk of heart failure. • Agents with documented effects on morbidity and mortality such as ACE inhibitors, β-blockers, and ARBs are recommended in patients with co-existing pulmonary disease.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management**[107] **(2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • Several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an ARB or a CCB, and in recent large-scale trials for the ACE inhibitor/CCB combination. The ARB/CCB combination also appears to be rational and effective. These combinations can be recommended for priority

Clinical Guideline	Recommendation(s)
	use. • Use of an ACE inhibitor/ARB combination may increase adverse events. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment. • Combination treatment is commonly needed to effectively lower blood pressure in diabetic patients. A renin–angiotensin receptor blocker should always be included because of the evidence of its protective effect against initiation or progression of nephropathy.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[35] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. • The choice of drug should depend on several factors, including previous patient response to a class of medications, the effect of a medication on cardiovascular risk according to the patient's cardiovascular profile, presence of compelling indications for certain medications, the presence of disorders which may limit the use of a class of medications, possibility of drug interactions, and side effects. • Drugs which exert their effects for 24 hours and can be given once daily should be preferred to enhance compliance. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors, ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end-stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the

Clinical Guideline	Recommendation(s)
	following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, and the combination is likely to be well tolerated.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[36] (2006)**	• Initial therapy in patients ≥55 years should be a calcium-channel blocking agent (CCB) or a thiazide diuretic, and in patients <55 years initial therapy should be an ACE inhibitor. If a second medication is required and the initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[33] (2004)**	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • In patients with acute coronary syndromes (myocardial infarction or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. • For patients with post-myocardial infarction, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood

Clinical Guideline	Recommendation(s)
	pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2-4 times higher in African American patients. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant. • ACE inhibitors should not be used in patients who have a history of angioedema.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[39] (2004)**	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. • Combination therapy is likely to be necessary to achieve blood pressure goals. If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible. • Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-myocardial infarction with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-myocardial infarction (β-blockers), chronic stable angina (CCBs, β-blockers), high CAD risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), and supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
World Health Organization (WHO)/International Society of Hypertension (ISH): **WHO/ISH Statement on Management of**	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific

Clinical Guideline	Recommendation(s)
Hypertension[34] **(2003)**	drug class include elderly patients with isolated systolic hypertension (diuretics, dihydropyridine CCBs), renal disease (ACE inhibitors, ARBs), post-myocardial infarction (ACE inhibitors, β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics, ACE inhibitors). • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[38] **(2003)**	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • African American patients appear to be at an increased risk for ACE inhibitor-associated cough, angioedema, or both. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[37] **(2010)**	Hypertension • Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. • If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate (GFR) is ≥30 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated GFR is <30 mL/min/1.73 m^2. • Multiple drugs are generally required to achieve blood pressure goals. Coronary Heart Disease • In patients with known cardiovascular disease and in patients >40 years with another cardiovascular risk factor, ACE inhibitor, aspirin, and statin therapy (if not contraindicated) should be used to reduce the risk of cardiovascular events. Diabetic Nephropathy • In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used. • In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. • In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBS have been shown to delay the progression to macroalbuminuria. • In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy. • If one class is not tolerated, the other should be substituted.

III. Indications

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

Table 3. FDA-Approved Indications for the Angiotensin-Converting Enzyme Inhibitors (Drugs B – F)[1-20]

Indication	Benazepril	Benazepril/ HCTZ	Captopril	Captopril/ HCTZ	Enalapril	Enalapril/ HCTZ	Fosinopril	Fosinopril/ HCTZ
Heart Failure								
Management of heart failure as adjunctive therapy when added to conventional therapy including diuretics with or without digitalis							✔	
Treatment of congestive heart failure, usually in combination with diuretics and digitalis			✔					
Treatment of congestive heart failure, usually in combination with diuretics and digitalis, to improve symptoms, increase survival, and decrease the frequency of hospitalization					✔			
Hypertension								
Treatment of hypertension	✔ *	✔ †	✔ *	✔	✔ *	✔ †	✔ *	✔ †
Left Ventricular Dysfunction								
To decrease the rate of development of overt heart failure and decrease the incidence of hospitalization for heart failure in clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction <35%)					✔			
Myocardial Infarction								
To improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction (ejection fraction <40%) and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure			✔					

*Alone or in combination with other antihypertensive agents.
†This fixed combination drug is not indicated for the initial therapy of hypertension.

Table 4. FDA-Approved Indications for the Angiotensin-Converting Enzyme Inhibitors (Drugs L – T)[1-20]

Indication	Lisino-pril	Lisinopril/ HCTZ	Moexi-pril	Moexipril/ HCTZ	Perindo-pril	Quina-pril	Quinapril/ HCTZ	Rami-pril	Trandola-pril	Trandolapril/ Verapamil
Cardiovascular Risk Reduction										
To reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients ≥55 years of age at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor								✔		
To reduce the risk of cardiovascular mortality or nonfatal myocardial infarction in patients with stable coronary artery disease					✔					
Heart Failure										
Management of heart failure as adjunctive therapy in patients who are not responding adequately to diuretics and digitalis	✔									
Management of heart failure as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis						✔				
To decrease the risk of death, heart failure-related hospitalization, and progression to severe/resistant heart failure in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction								✔		
Hypertension										
Treatment of hypertension	✔ *	✔ †	✔ *	✔ †	✔ *	✔ *	✔ †	✔ *	✔ *	✔ †
Myocardial Infarction										
To decrease the risk of death and heart failure-related hospitalization in stable patients who have left ventricular systolic dysfunction or who are symptomatic from congestive heart failure within the first few days after acute myocardial infarction									✔	
Treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction to improve survival	✔									

*Alone or in combination with other antihypertensive agents.
†This fixed combination drug is not indicated for the initial therapy of hypertension.

IV. Pharmacokinetics

The pharmacokinetic parameters of the angiotensin-converting enzyme inhibitors are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Angiotensin-Converting Enzyme Inhibitors[1-20]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Benazepril	37	96.7	Liver, extensive	Renal (33) Bile (12)	22*
Captopril	70-75	25-30	Liver (50)	Renal (95)	1.9†
Enalapril	60	50-60	Liver (70)	Renal (61) Feces (33)	11*
Fosinopril	30-36	89-100	Liver, extensive	Renal (44) Feces (46)	12*
Lisinopril	25	Minimal	Liver (7)	Renal (29) Feces (69)	12†
Moexipril	13-22	50-70	Liver, extensive	Renal (13) Feces (50)	2-10*
Perindopril	20-30	60	Liver (88-96)	Renal (75) Feces (25)	3-10*
Quinapril	50	97	Liver, extensive	Renal (50-60) Feces (33)	2-25*
Ramipril	60	73	Liver, extensive	Renal (40-60) Feces (40)	13-17*
Trandolapril	10	80	Liver, extensive	Feces (66) Renal (33)	16-24*
Hydrochlorothiazide	50-75	40-68	Not metabolized	Renal (>95)	6-15
Verapamil	20-35	88-94	Liver (65-80)	Renal (70) Feces (9-16)	4-12

†Parent compound
*Metabolites

V. Drug Interactions

Significant drug interactions with the angiotensin-converting enzyme inhibitors are listed in Table 6.

Table 6. Significant Drug Interactions with the Angiotensin-Converting Enzyme Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	1	Potassium-sparing diuretics	Combining ACE inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentrations in certain high-risk patients.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics increase potassium excretion. Hypokalemia may occur, increasing the risk of torsades de pointes.
Hydrochlorothiazide	1	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has

Generic Name(s)	Significance Level	Interaction	Mechanism
			occurred.
Verapamil	1	β-Blockers	Verapamil may inhibit oxidative metabolism of certain β-blockers. The effects of both drugs may be increased.
Verapamil	1	Colchicine	Plasma concentrations of colchicine may be increased by verapamil. Colchicine toxicity may occur.
Verapamil	1	Dofetilide	Verapamil can increase portal blood flow, increasing the rate of dofetilide absorption. There may be an increased risk of ventricular arrhythmias, including torsades de pointes.
Verapamil	1	Macrolides and ketolides	Macrolides and ketolides may increase the plasma concentrations and pharmacological effects of verapamil.
Verapamil	1	Narcotic analgesics	Verapamil may increase plasma concentrations of narcotic analgesics when used concurrently.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	Aliskiren	The risk of hyperkalemia may be increased when ACE inhibitors are combined with aliskiren.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	Angiotensin II receptor antagonists	The risk of hyperkalemia may be increased when ACE inhibitors are combined with angiotensin II receptor antagonists.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	Indomethacin	Indomethacin inhibits prostaglandin synthesis. The hypotensive effect of ACE inhibitors may be reduced.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril)	2	Lithium	Through an unknown mechanism, ACE inhibitors may increase lithium levels, which results in neurotoxicity.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	NSAIDs and salicylates	NSAIDs and salicylates inhibit prostaglandin synthesis. The hypotensive and vasodilator effects of the ACE inhibitor may be reduced.
ACE inhibitors (benazepril, captopril,	2	Potassium preparations	Hyperkalemia, possibly with cardiac arrhythmias or cardiac

Generic Name(s)	Significance Level	Interaction	Mechanism
enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)			arrest, may occur with the combination of ACE inhibitors and potassium preparations.
ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	2	Trimethoprim	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of ACE inhibitors and trimethoprim.
Hydrochlorothiazide	2	Diazoxide	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Hydrochlorothiazide	2	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.
Verapamil	2	Aldosterone blockers	Plasma concentrations and pharmacologic or toxic effects of aldosterone blockers may be increased by verapamil.
Verapamil	2	Carbamazepine	Verapamil appears to impair the hepatic metabolism of carbamazepine. Carbamazepine levels may increase, resulting in an increase in pharmacologic and toxic effects.
Verapamil	2	Clonidine	Sinus bradycardia, AV block and severe hypotension may occur with coadministration of clonidine and verapamil.
Verapamil	2	Cyclosporine	Verapamil may inhibit cyclosporine metabolism leading to increased cyclosporine levels and toxicity.
Verapamil	2	Digitalis glycosides	Verapamil may alter the pharmacokinetics and increase serum concentrations of digoxin.
Verapamil	2	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by verapamil. Dronedarone may also increase the plasma concentrations and pharmacologic effects of verapamil.
Verapamil	2	Everolimus	Pharmacologic effects and plasma concentrations of everolimus may be increased by verapamil.
Verapamil	2	Flecainide	Increased risk of cardiotoxic effects may occur when flecainide and verapamil are coadministered.
Verapamil	2	HMG-CoA reductase inhibitors	Verapamil may inhibit the first-pass metabolism of certain

Generic Name(s)	Significance Level	Interaction	Mechanism
			HMG-CoA reductase inhibitors (e.g., simvastatin and lovastatin) which results in increased plasma concentrations and risk of toxicity.
Verapamil	2	Nondepolarizing muscle relaxants	The effects of the nondepolarizing muscle relaxants may be enhanced and respiratory depression may be prolonged. The mechanism probably involves blockade of calcium-channels in skeletal muscle at the postsynaptic muscle membrane site.
Verapamil	2	Quinidine	Verapamil can prolong the half-life of quinidine by interfering with clearance. There is an increased risk for hypotension, bradycardia, ventricular tachycardia and atrioventricular block.
Verapamil	2	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased by co-administration of verapamil.
Verapamil	2	Rifampin	First-pass hepatic metabolism of verapamil may be increased, resulting in lowered bioavailability and reduced effectiveness of oral verapamil.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the angiotensin-converting enzyme inhibitors are listed in Table 7. The most common adverse drug events reported with hydrochlorothiazide and verapamil are listed in Table 8. The boxed warning for the angiotensin-converting enzyme inhibitors is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Angiotensin-Converting Enzyme Inhibitors[1-20]

Adverse Events	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Cardiovascular										
Angina	<1	<1	2	<1	-	<1	-	<1	<1-3	-
Bradycardia	-	-	<1	<1	<1	-	-	-	<1	<5
Cardiac arrest	-	✔	<1	✔	<1	-	✔	-	✔	-
Cerebrovascular accident	-	✔	<1	<1	<1	<1	<1	<1	<1	-
Chest pain	-	1	2	<2	3	>1	2	2	<1	<1
Hypotension	<1	✔	1-7	1-4	1-10	<1	<1	3	<1	<1
Myocardial infarction	-	<1	<1	<1	<1	<1	<1	<1	<1	-
Orthostatic hypotension	<1	✔	1-2	<2	<1	<1	<1	<1	2	-
Palpitations	<1	1	<1	<1	<1	<1	<1	<1	<1	<1
Peripheral edema	<1	-	-	-	<1	>1	-	-	-	-
Rhythm disturbances	-	✔	<1	<1	-	<1	-	<1	-	-
Tachycardia	-	1	<1	<1	<1	-	-	<1	<1	-
Central Nervous System										
Anxiety	<1	-	-	-	-	<1	<1	-	<1	<1
Ataxia	-	✔	<1	-	<1	-	-	-	-	-
Depression	-	✔	<1	<1	-	-	2	<1	<1	-
Dizziness	4	-	1-8	2-12	5-12	4	8	4-8	2-4	1-23
Fatigue	2	-	1-3	≥1	3	2	-	3	2	-
Headache	6	-	2-5	≥1	4-6	>1	24	2	-	-
Insomnia	<1	-	<1	<1	<1	<1	3	<1	<1	<1
Malaise	-	-	-	-	<1	<1	<1	<1	<1	-
Nervousness	<1	✔	<1	-	<1	<1	1	<1	<1	-
Paresthesias	<1	-	<1	<1	<1	-	2	<1	<1	<1
Peripheral edema	<1	-	-	-	-	>1	-	-	-	-
Somnolence/drowsiness	2	✔	<1	<1	<1	<1	1	<1	<1	<1
Vertigo	-	-	2	<1	<1	-	<1	<1	<1-2	<1
Dermatologic										
Alopecia	<1	-	<1	-	<1	<1	-	<1	-	-
Diaphoresis	<1	-	<1	<1	<1	<1	<1	<1	<1	-
Erythema multiforme	-	✔	<1	-	-	-	<1	-	<1	-
Exfoliative dermatitis	-	✔	<1	✔	-	-	✔	<1	-	-

Adverse Events	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Flushing	<1	<1	<1	<1	<1	2	-	-	-	<1
Pemphigus/pemphigoid	<1	✔	<1	-	<1	-	-	<1	-	<1
Photosensitivity	<1	✔	<1	<1	<1	<1	-	<1	-	-
Pruritus	<1	2	<1	<1	-	<1	<1	<1	<1	<1
Rash	<1	4-7	<1	<1	<1	2	2	1	<1	<1
Stevens-Johnson syndrome	<1	✔	<1	-	✔	-	-	-	<1	-
Toxic epidermal necrolysis	-	-	<1	-	✔	-	-	-	<1	-
Urticaria	-	-	<1	<1	<1	<1	-	<1	<1	-
Gastrointestinal										
Abdominal pain	-	-	2	<1	2	<1	3	1	<1	<1
Anorexia	-	-	<1	-	-	-	-	-	<1	-
Constipation	<1	-	<1	<1	<1	<1	<1	<1	<1	<1
Diarrhea	-	-	1-2	>1	3-4	3	4	2	≤1	<1
Dry mouth	-	-	<1	<1	<1	<1	<1	<1	<1	-
Dysgeusia	-	2-4	-	-	-	-	-	-	-	-
Dyspepsia	-	✔	<1	-	<1	>1	<1	<1	<1	<6
Hepatitis	-	✔	<1	<1	<1	<1	-	<1	<1	-
Nausea	1	-	1	1-2	2	>1	2	2	2	-
Pancreatitis	<1	✔	<1	<1	<1	<1	✔	<1	<1	<1
Vomiting	<1	-	1	1-2	<1	<1	2	2	2	<1
Genitourinary										
Decreased libido	<1	-	-	<1	<1	-	-	-	-	<1
Impotence	<1	✔	<1	-	1	-	-	<1	<1	<1
Oliguria	-	<1	<1	-	<1	<1	-	-	-	-
Urinary tract infection	<1	-	1	-	<1	-	3	<1	-	-
Musculoskeletal										
Arthralgia	<1	✔	✔	<1	<1	<1	<1	<1	<1	-
Arthritis	<1	-	✔	✔	<1	-	1	-	<1	-
Muscle cramps	-	-	<1	<1	<1	-	-	-	-	<1
Myalgia	<1	✔	✔	<1	<1	1	<1	-	<1	5
Respiratory										
Asthma	<1	✔	<1	-	<1	-	-	-	-	-
Bronchitis	<1	-	1	-	<1	-	<1	-	-	-
Bronchospasm	-	✔	<1	<1	<1	<1	-	2-4	-	-
Cough	1	<2	1-2	2-10	1-4	6	6-12	2-4	8	2-35
Dyspnea	<1	-	1	≥1	<1	<1	<1	-	<1	<1
Pharyngitis	-	-	-	<1	<1	2	3	<1	-	-

Adverse Events	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Moexipril	Perindopril	Quinapril	Ramipril	Trandolapril
Rhinitis	-	✔	-	<1	<1	>1	5	-	-	-
Sinusitis	<1	-	-	<1	<1	>1	<5	-	-	-
Upper respiratory tract infection	-	-	<1	2	2	>1	7	-	✔	<1
Miscellaneous										
Anemia	✔	<1	-	✔	<1	<1	-	<1	<1	-
Angioedema	<1	<1	✔	<1	<1	<1	<1	<1	<1	<1
Asthenia	<1	✔	1-2	-	1	-	8	-	2	3
Blurred vision	-	✔	<1	-	<1	-	-	-	-	-
Eosinophilia	-	✔	✔	✔	<1	-	-	-	<1	-
Fever	-	✔	<1	<1	<1	-	<1	-	<1	-
Syncope	<1	✔	1-2	<1	<2	<1	<1	<1	<2	6
Tinnitus	-	-	<1	<1	<1	<1	2	-	<1	-
Vasculitis	-	✔	✔	-	<1	-	✔	-	<1	-

✔ Percent not specified
- Event not reported

Table 8. Adverse Drug Events (%) Associated With Hydrochlorothiazide and Verapamil[1-20]

Adverse Events	Hydrochlorothiazide	Verapamil
Cardiovascular		
Angina	-	≤1
Atrioventricular block	-	<2
Bradycardia	-	1
Chest pain	-	≤1
Congestive heart failure	-	2
Edema	-	2-3
Electrocardiogram abnormalities	-	2
Hypertension	-	2
Hypotension	1-10	<3
Myocardial infarction	-	≤1
Palpitations	-	≤1
Peripheral edema	-	4
Syncope	-	≤1
Tachycardia	-	1
Vasculitis	-	≤1
Central Nervous System		
Asthenia	-	2
Confusion	-	≤1
Depression	-	✔
Dizziness	-	3-5
Equilibrium disturbances	-	≤1
Fatigue	-	2-5
Headache	-	2-12
Insomnia	-	≤1
Paresthesia	-	≤1
Shakiness/jitteriness	-	≤1
Sleep disturbances	-	1
Somnolence	-	≤1
Vertigo	-	✔
Weakness	✔	-
Dermatologic		
Alopecia	<1	≤1
Bruising	-	≤1
Dermatitis	-	-
Erythema multiforme	<1	≤1
Exfoliative dermatitis	<1	-
Flushing	-	<1
Photosensitivity	1-10	-
Rash	-	<2
Urticaria	-	≤1
Endocrine and Metabolic		
Glycosuria	✔	-
Hypercalcemia	<1	-
Hyperglycemia	✔	-
Hyperuricemia	✔	-
Hypokalemia	1-10	-
Liver enzymes elevated	-	1
Gastrointestinal		
Anorexia	1-10	-
Constipation	-	4-12
Cramping	✔	-

Adverse Events	Hydrochlorothiazide	Verapamil
Diarrhea	-	≤2
Dry mouth	-	≤1
Dyspepsia	-	3
Epigastric distress	1-10	-
Gastric irritation/distress	✔	≤1
Gingival hyperplasia	-	≤1
Hepatic function impairment	✔	-
Jaundice	✔	-
Nausea	-	2-3
Pancreatitis	<1	-
Sialadenitis	✔	-
Genitourinary		
Impotence	-	≤1
Interstitial nephritis	<1	-
Renal dysfunction	✔	-
Renal failure	<1	-
Urinary frequency	-	≤1
Hematologic		
Agranulocytosis	✔	-
Aplastic anemia	<1	-
Ecchymosis	-	≤1
Hemolytic anemia	<1	-
Leukopenia	<1	-
Purpura	-	≤1
Thrombocytopenia	<1	-
Musculoskeletal		
Arthralgia	1-2	≤1
Muscle cramps	-	≤1
Muscle spasm	✔	-
Myalgia	-	1.1
Sweating	-	≤1
Respiratory		
Dyspnea	-	1
Pharyngitis	-	3
Respiratory distress	<1	2
Respiratory failure	-	✔
Rhinitis	-	3
Sinusitis	-	3
Miscellaneous		
Abnormal/transient blurred vision	✔	≤1
Accidental injury	-	2
Allergic myocarditis	<1	-
Allergic reactions	<1	-
Allergy aggravated	-	≤2
Fever	✔	-
Flu-like illness/ syndrome/symptoms	-	4
Flushing	-	<1
Infection	-	12
Necrotizing angiitis	✔	-
Purpura	✔	-
Tinnitus	-	≤1
Xanthopsia	✔	-

✔ Percent not specified
- Event not reported

Table 9. Boxed Warning for the Angiotensin-Converting Enzyme Inhibitors[1]

WARNING
Use in pregnancy: When used in pregnancy during the second and third trimesters, angiotension-converting enzyme (ACE) inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, discontinue benazepril as soon as possible.

VII. Dosing and Administration

The usual dosing regimens for the angiotensin-converting enzyme inhibitors are listed in Table 10.

Table 10. Usual Dosing Regimens for the Angiotensin-Converting Enzyme Inhibitors[1-20]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Benazepril	Hypertension: Initial: 10 mg once daily (for patients not receiving diuretics); maintenance: 20 to 40 mg per day as a single dose or in 2 equally divided doses; total daily doses above 80 mg have not been evaluated	Children 7-16 years of age: Hypertension: Initial, 0.2 mg/kg once daily; doses above 0.6 mg/kg (or in excess of 40 mg daily) have not been studied	Tablet: 5 mg 10 mg 20 mg 40 mg
Benazepril and hydrochlorothiazide	Hypertension: Fixed-combination drug is not indicated for initial therapy; switch to 10 mg-12.5 mg or 20 mg-12.5 mg per day if not adequately controlled on benazepril monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 5 mg-6.25 mg 10 mg-12.5 mg 20 mg-12.5 mg 20 mg-25 mg
Captopril	Heart Failure: Initial: 25 mg 3 times a day; maximum: 450 mg daily Hypertension: Initial: 25 mg 2 to 3 times per day; after 1 to 2 weeks, can increase to 50 mg 2 to 3 times per day; maximum: 450 mg daily Post-Myocardial Infarction: Initial: single dose of 6.25 mg then 12.5 mg 3 times a day; target maintenance: 50 mg 3 times a day	Safety and efficacy in children have not been established.	Tablet: 12.5 mg 25 mg 50 mg 100 mg
Captopril and hydrochlorothiazide	Hypertension: Initial: 25 mg-5 mg once daily; titrate with individual components or fixed-combination; combination may be substituted for the titrated individual	Safety and efficacy in children have not been established.	Tablet: 25 mg-15 mg 25 mg-25 mg 50 mg-15 mg 50 mg-25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	components; in general, daily doses of captopril and HCTZ should not exceed 150 mg and 50 mg, respectively		
Enalapril	Heart Failure: Initial: 2.5 mg; maintenance: 2.5 to 20 mg 2 times a day; maximum: 40 mg daily in divided doses Hypertension: Initial: 5 mg once daily; maintenance: 10 to 40 mg per day as a single dose or in 2 divided doses Left Ventricular Dysfunction: Initial: 2.5 mg 2 times a day; target maintenance: 20 mg in divided doses	Children 1 month to 16 years of age: Hypertension: Initial, 0.08 mg/kg (up to 5 mg) once daily; doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied	Tablet: 2.5 mg 5 mg 10 mg 20 mg
Enalapril and hydrochlorothiazide	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum: 4 tablets of 5 mg-12.5 mg or 2 tablets of 10 mg-25 mg	Safety and efficacy in children have not been established.	Tablet: 5 mg-12.5 mg 10 mg-25 mg
Fosinopril	Heart failure: Initial: 10 mg once daily; maintenance: 20 to 40 mg daily; maximum: 40 mg once daily Hypertension: Initial: 10 mg once daily; maintenance: 20 to 40 mg daily (single or divided doses); maximum: 80 mg daily	Children 6-16 years of age: Hypertension: >50 kg: 5 to 10 mg once daily	Tablet: 10 mg 20 mg 40 mg
Fosinopril and hydrochlorothiazide	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect	Safety and efficacy in children have not been established.	Tablet: 10 mg-12.5 mg 20 mg-12.5 mg
Lisinopril	Heart failure: Initial: 5 mg once daily; maintenance: 5 to 20 mg once daily Hypertension: Initial: 10 mg once daily; maintenance: 20 to 40 mg	Children 6-16 years of age: Hypertension: Initial: 0.07 mg/kg (up to 5 mg) once daily; doses >0.61 mg/kg (or in excess of 40 mg) have not been studied	Tablet: 2.5 mg 5 mg 10 mg 20 mg 30 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	once daily Post-Myocardial Infarction: Initial: 5 mg every 24 hours for 2 doses, then 10 mg every day for 6 weeks		
Lisinopril and hydrochlorothiazide	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 10 mg-12.5 mg or 20 mg-12.5 mg after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; maximum: lisinopril 80 mg and HCTZ 50 mg per day	Safety and efficacy in children have not been established.	Tablet: 10 mg-12.5 mg 20 mg-12.5 mg 20 mg-25 mg
Moexipril	Hypertension: Initial: 7.5 mg once daily; maintenance: 7.5 to 30 mg daily, administered in one or two divided doses; maximum: 60 mg per day	Safety and efficacy in children have not been established.	Tablet: 7.5 mg 15 mg
Moexipril and hydrochlorothiazide	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 7.5 mg-12.5 mg, 15 mg-12.5 mg or 15 mg-25 mg after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; maximum: lisinopril 30 mg and HCTZ 50 mg per day	Safety and efficacy in children have not been established.	Tablet: 7.5 mg-12.5 mg 15 mg-12.5 mg 15 mg-25 mg
Perindopril	Coronary Artery Disease: Initial: 4 mg once daily for 2 weeks; increase as tolerated to 8 mg once daily Hypertension: Initial: 4 mg once daily; maintenance: 4 to 8 mg daily as a single or divided dose; maximum: 16 mg per day	Safety and efficacy in children have not been established.	Tablet: 2 mg 4 mg 8 mg
Quinapril	Heart failure: Initial: 5 mg twice daily; titrate at weekly intervals to 10 to 20 mg 2 times a day Hypertension: Initial: Start with 10 to 20 mg once daily; titrate at intervals	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	of at least 2 weeks; maintenance: 20 to 80 mg per day in single or 2 equally divided doses		
Quinapril and hydrochlorothiazide	Hypertension: Fixed-combination drug is not indicated for initial therapy; initiate combination therapy on 10 mg-12.5 mg or 20 mg-12.5 mg after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 10 mg-12.5 mg 20 mg-12.5 mg 20 mg-25 mg
Ramipril	Cardiovascular Risk Reduction: Initial: 2.5 mg once daily for 1 week, then 5 mg once daily for 3 weeks; maintenance, 10 mg once daily Heart failure: Initial: 2.5 mg twice daily; target dose, 5 mg twice daily Hypertension: Initial: 2.5 mg once daily; maintenance: 2.5 to 20 mg per day in single or 2 equally divided doses	Safety and efficacy in children have not been established.	Capsule: 1.25 mg 2.5 mg 5 mg 10 mg Tablet: 1.25 mg 2.5 mg 5 mg 10 mg
Trandolapril	Post-Myocardial Infarction: Initial: 1 mg once daily; titrate as tolerated to target of 4 mg once daily Hypertension: Initial: 1 mg once daily in non-African American patients and 2 mg once daily in African American patients; titrate dose at 1-week intervals; maintenance: 2 to 4 mg once daily	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg
Trandolapril and verapamil	Hypertension: Fixed-combination drug is not indicated for initial therapy; combination may be substituted for the titrated individual components; usual dosage range for trandolapril for hypertension is 1-4 mg per day in 1or 2 divided doses and for verapamil extended-release 120 to 480 mg per day in 1 or 2 divided doses	Safety and efficacy in children have not been established.	Tablet (ER): 1 mg-240 mg 2 mg-180 mg 2 mg-240 mg 4 mg-240 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the angiotensin-converting enzyme inhibitors are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Angiotensin-Converting Enzyme Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Disease				
Swedberg et al.[43] (1992) CONSENSUS II Enalapril 5 to 20 mg/day vs placebo Treatment was started with an intravenous infusion of 1mg of enalaprilat administered over 3 hours followed by oral enalapril 6 hours after the infusion was stopped.	DB, MC, PC, PG, RCT Patients who presented within 24 hours of the onset of acute myocardial infarction symptoms	N=6,090 180 days	Primary: Mortality rates within 6 months Secondary: Mortality within 1 month, cause of death, re-infarction, or worsening heart failure	Primary: Mortality rates according to life-table analysis between the enalapril and placebo groups at 6 months were not significantly different (11% vs 10.2%; P=0.26). The relative risk associated with enalapril treatment and based on the mortality curves was 1.10 (95% CI, 0.93 to 1.29). Secondary: Mortality rates between the enalapril and placebo groups at 1 month were not significantly different (7.2% vs 6.3%; P=0.26). Death due to progressive heart failure occurred more frequently in patients treated with enalapril than placebo (4.3% vs 3.4%; P=0.06). There were no significant differences in the rate of reinfarction between the enalapril or placebo groups (P=NS). Change in therapy because of heart failure occurred more in the placebo group (P<0.006) but there were no significant differences in hospitalization for heart failure (P=NS). Note: The first CONSENSUS trial excluded patients with a recent myocardial infarction or unstable angina. The study was stopped early after recruiting 6,090 of the intended 9,000 patients since more patients had died on the drug than on placebo (although the difference was not statistically significant).
Nissen et al.[51] (2004) CAMELOT Enalapril 10 to 20	DB, MC, PC, RCT Patients 30 to 79 years of age requiring coronary	N=1,991 2 years	Primary: Composite of cardiovascular events (cardiovascular death, nonfatal	Primary: Cardiovascular events occurred in 23.1% of placebo-treated patients, 16.6% amlodipine-treated patients (HR, 0.69; 95% CI, 0.54 to 0.88; P=0.003) and 20.2% enalapril-treated patients (HR, 0.85; 95% CI, 0.67 to 17; P=0.16).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs amlodipine 5 to 10 mg/day vs placebo	angiography for evaluation for chest pain or PCI and a diastolic pressure <100 mm Hg, with or without treatment		myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for CHF, fatal or nonfatal stroke or TIA, and any new diagnosis of PVD), nominal change in percent atheroma volume (substudy) Secondary: Incidence of adverse events; all-cause mortality, incidence of revascularization in vessels that had undergone previous stent placement	The primary end point comparison for enalapril vs amlodipine was not significant (HR, 0.81; 95% CI, 0.63 to 14; P=0.10). Secondary: Coronary revascularization was reduced in the amlodipine group from 15.7% to 11.8% (HR, 0.73; 95% CI, 0.54 to 0.98; P=0.03). Hospitalization for angina was reduced in the amlodipine group from 12.8% to 7.7% (HR, 0.58; 95% CI, 0.41 to 0.82; P=0.002). Individual components of the primary end point generally showed fewer events with enalapril treatment vs placebo, but none of the comparisons reached statistical significance. For components of the primary end point, only the rate of hospitalization for angina showed a statistically significant difference between amlodipine and enalapril (HR, 0.59; 95% CI, 0.42 to 0.84; P=0.003). A trend toward fewer episodes of revascularization in patients undergoing intervention at baseline was observed for amlodipine vs enalapril (HR, 0.66; 95% CI, 0.40 to 16; P=0.09). The mean change in percent atheroma volume was 0.5% for amlodipine (P=0.12 vs placebo), 0.8% for enalapril (P=0.32 vs placebo) and 1.3% for placebo. In patients with systolic blood pressure greater than the mean, the amlodipine group showed a significantly slower progression (0.2%) compared with placebo (2.3%; P=0.02). Compared with baseline, intravascular ultrasound showed progression in patients receiving placebo (P<0.001), a trend toward progression with enalapril (P=0.08) and no progression in patients receiving amlodipine (P=0.31). For the amlodipine group, correlation between blood pressure reduction and progression was r=0.19 (P=0.07). Discontinuation from the study for treatment-emergent adverse events was low, averaging 0.4% and not statistically significant between the 3 treatment groups. The only statistically significant difference in secondary end points was that amlodipine demonstrated a significant reduction in revascularization

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				after previous stent placement compared with placebo (4.1% vs 7.9%; HR, 0.49; 95% CI, 0.31 to 0.78; P=0.002). The rate of revascularization was lower than enalapril (6.2%) but not statistically significant (HR 0.66, 95% CI, 0.40 to 16; P=0.09).
Fox et al.[44] (2003) EUROPA Perindopril 8 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with evidence of CHD (e.g., myocardial infarction >3 months before screening, percutaneous or surgical coronary revascularization >6 months before screening, 70% narrowing of 1 or more major coronary arteries, history of chest pain) and without clinical heart failure or uncontrolled hypertension	N=12,218 4.2 years (mean)	Primary: Composite of cardiovascular death, myocardial infarction, or cardiac arrest Secondary: Composite of total mortality, nonfatal myocardial infarction, hospital admission for unstable angina, and cardiac arrest with successful resuscitation; cardiovascular mortality and nonfatal myocardial infarction; individual components of the secondary outcomes and revascularization, stroke, and admission for heart failure	Primary: Patients treated with perindopril had a significant reduction in the primary outcome compared to patients treated with placebo (8% vs 10%; RR reduction, 20%; 95% CI, 9% to 29%; P=0.0003). The benefit began to appear at 1 year and gradually increased throughout the trial. Secondary: Compared with placebo, treatment with perindopril was associated with reductions in all secondary end points. However, not all changes were significant. There was a 14% reduction in total mortality, nonfatal myocardial infarction, unstable angina, and cardiac arrest (P=0.0009). There was a 22% reduction in nonfatal myocardial infarction with perindopril (P=0.001). Total mortality was 11% lower with perindopril but this finding was not significant (P=0.1). Hospital admission for heart failure was significantly reduced with perindopril by 39% (P=0.002).
PREAMI Investigators[45] (2006)	DB, MC, PC, PG, RCT	N=1,252 12 months	Primary: Composite of death,	Primary: The primary end point occurred in 35% of patients taking perindopril and 57% of patients on placebo, with an absolute risk reduction of 0.22 (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Perindopril 8 mg/day vs placebo	Patients ≥65 years with LVEF ≥40% and recent acute myocardial infarction		hospitalization for heart failure or left ventricular remodeling Secondary: Cardiovascular death, hospitalization for reinfarction or angina, revascularization	CI, 0.16 to 0.28; P<0.001). A total of 126 patients (28%) and 226 patients (51%) in the perindopril and placebo groups, respectively, experienced remodeling (P<0.001). The mean increase in left ventricular end-diastolic volume was 0.7 mL with perindopril compared with 4.0 mL with placebo (P<0.001). Secondary: Cardiovascular death, hospitalization for subsequent acute myocardial infarction or angina or revascularization was infrequent and not modified by treatment. Conclusion: Perindopril treatment for 1 year reduced progressive left ventricular remodeling but was not associated with better clinical outcomes.
HOPE Investigators[47] (2000) Ramipril 10 mg QD vs placebo	DB, RCT, two-by-two factorial trial Men and women ≥55 years old with history of CAD, stroke, PVD, or diabetes and at least one other cardiovascular risk factor and who were not known to have a low ejection fraction (<40%) or heart failure	N=9,297 5 years (mean)	Primary: Composite of death from cardiovascular causes, myocardial infarction, or stroke and each outcome separately Secondary: Death from any cause, revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes Other end points: Worsening angina, cardiac arrest,	Primary: Fewer patients on ramipril than placebo (14.0% vs 17.8%, respectively) died of cardiovascular causes or had a myocardial infarction or stroke (RR, 0.78; 95% CI, 0.70 to 0.86; P<0.001). Treatment with ramipril reduced the rates of death from cardiovascular causes (RR, 0.74; P<0.001), myocardial infarction (RR, 0.80; P<0.001), and stroke (RR, 0.68; P<0.001). Secondary: The risk of death from any cause was also significantly reduced by treatment with ramipril (RR, 0.84; P=0.005). Significantly fewer patients treated with ramipril underwent revascularization compared with placebo (RR, 0.85; P=0.002). Fewer hospitalizations for heart failure were reported with ramipril vs placebo but the risk reduction was not statistically significant (RR, 0.88; P=0.25). Fewer complications related to diabetes were reported in patients receiving ramipril (RR, 0.84; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			heart failure, unstable angina with ECG changes, and the development of diabetes	Other end points: Significantly fewer patients treated with ramipril than placebo group had the following: worsening angina (RR, 0.89; P=0.004), cardiac arrest (RR, 0.62; P=0.02), heart failure (RR 0.77; P<0.001), and new diagnosis of diabetes (RR, 0.66; P<0.001). There was no difference between treatment groups for unstable angina with ECG changes (RR, 0.97; P=0.76).
ONTARGET Investigators[48] (2008) Ramipril 10 mg/day vs telmisartan 80 mg/day vs ramipril 10 mg/day and telmisartan 80 mg/day	DB, MC, PC, RCT Patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	N=25,620 56 months (median follow-up)	Primary: Death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure Secondary: Composite of death from cardiovascular causes, myocardial infarction or stroke; heart failure, worsening or new angina, new diagnosis diabetes mellitus, new atrial fibrillation, renal impairment, revascularization procedures	Primary: The primary outcome occurred in 16.5%, 16.7% and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively. Secondary: The composite of death from cardiovascular causes, myocardial infarction or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 17; P=0.001 for non-inferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 17). There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (P<0.001 vs ramipril; no P value reported vs telmisartan). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs 4.2%; P<0.001) and angioedema (0.1% vs 0.3%; P=0.01) and a higher rate of hypotensive symptoms (2.6% vs 1.7%; P<0.001); the rate of syncope was the same in the 2 groups (0.2%). As compared with the ramipril group, combination therapy had an increased risk of hypotensive symptoms (4.8% vs 1.7%; P<0.001), syncope (0.3% vs 0.2%; P=0.03) and renal dysfunction (13.5% vs 10.2%; P<0.001).
PEACE Trial Investigators[49] (2004)	DB, PC, RCT Patients ≥50 years of age with stable CAD	N=8,290 4.8 years (median)	Primary: Combined rate of nonfatal myocardial	Primary: No significant differences in the primary outcome measures between trandolapril and placebo were reported (21.9% vs 22.5%; HR, 0.96; 95% CI, 0.88 to 16; P=0.43).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PEACE Trandolapril 4 mg/day vs placebo	and normal or slightly reduced left ventricular function (LVEF >40%)		infarction, death from cardiovascular causes, or coronary revascularization procedures Secondary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, unstable angina, new CHF, stroke, PVD, and cardiac arrhythmia	Secondary: No significant differences in secondary outcome measures between trandolapril and placebo were reported (P>0.05). Side effects leading to discontinuation of study medication occurred in 14.4% of patients receiving trandolapril and 6.5% of patients receiving placebo (P<0.001). The rates of cough (39.1% vs 27.5%; P<0.01) and syncope (4.8% vs 3.9%; P=0.04) were higher in patients receiving trandolapril vs placebo. Note: This trial was conducted in low-risk patients with stable CAD and normal or slightly reduced left ventricular function. However, the HOPE trial was conducted in patients with coronary or other vascular disease or with diabetes and another cardiovascular risk factor and the EUROPA trial was conducted in patients with evidence of CHD.
Pilote et al.[50] (2004) Captopril (50 mg), enalapril (10 mg), fosinopril (10 mg), lisinopril (10 mg), perindopril (4 mg), quinapril (20 mg), and ramipril (5 mg)	RETRO Patients ≥65 years who were hospitalized for acute myocardial infarction and filled a prescription for an ACE inhibitor within 30 days of discharge and who continued to receive the same drug for at least 1 year	N=7,512 Average of 2.3 years since discharge	Primary: 1-year mortality following an acute myocardial infarction Secondary: Readmissions due to cardiac complications	Primary: Captopril (HR, 1.56; 95% CI, 1.13 to 2.15), enalapril (HR, 1.47; 95% CI, 1.14 to 1.89), fosinopril (HR, 1.71; 95% CI, 1.29 to 2.25), lisinopril (HR, 1.28; 95% CI, 0.98 to 1.67) and quinapril (HR, 1.58; 95% CI, 1.10 to 2.82) were associated with higher mortality than was ramipril. No statistically significant difference was reported between perindopril and ramipril (HR, 0.98; 95% CI, 0.60 to 1.60). Secondary: Enalapril (HR, 1.44; 95% CI, 13 to 2.01) and fosinopril (HR, 1.83; 95% CI, 1.27 to 2.62) were associated with higher readmission rates for CHF than ramipril. Readmissions for unstable angina and recurrent myocardial infarction were similar across all prescription groups.
Dalhof et al.[52] (2005) ASCOT-BPLA	MC, OL, RCT Patients 40-79 years of age with	N=19,257 5.5 years	Primary: Nonfatal myocardial infarction	Primary: No statistically significant difference in nonfatal myocardial infarction and fatal CHD was reported between the amlodipine plus perindopril group compared to the atenolol plus bendroflumethiazide groups (HR, 0.90; 95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amlodipine 5 to 10 mg/day adding perindopril 4 to 8 mg/day as needed vs atenolol 50 to 100 mg/day adding bendro-flumethiazide 1.25 to 2.5 mg/day and potassium as needed If blood pressure was still not achieved, doxazosin 4 to 8 mg/day was added to the regimen.	hypertension and at least 3 other cardiovascular risk factors (left ventricular hypertrophy, other specified abnormalities on ECG, type 2 diabetes, PAD, history of stroke or TIA, male, age ≥55 years, microalbuminuria or proteinuria, smoking, total cholesterol to HDL-C ratio ≥6, or family history of CHD)		(including silent myocardial infarction) and fatal CHD Secondary: All-cause mortality, total stroke, primary end points minus silent myocardial infarction, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, nonfatal and fatal heart failure, effects on primary end point and on total cardiovascular events and procedures among prespecified subgroups Tertiary: Silent myocardial infarction, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias,	CI, 0.79 to 12; P=0.1052). Secondary: Significantly greater reductions in the following secondary end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: all- cause mortality (P=0.0247), total stroke (P=0.0003), primary end points minus silent myocardial infarction (P=0.0458), all coronary events (P=0.0070), total cardiovascular events and procedures (P<0.0001), and cardiovascular mortality (P=0.0010). There were no significant differences in nonfatal and fatal heart failure between the two treatment groups (P=0.1257). The study was terminated early due to higher mortality and worse outcomes on several secondary end points observed in the atenolol study group. Tertiary: Significantly greater reductions in the following end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: unstable angina (P=0.0115), PAD (P=0.0001), development of diabetes (P<0.0001), and development of renal impairment (P=0.0187). There were no significant differences in the incidence of silent myocardial infarction (P=0.3089), chronic stable angina (P=0.8323) or life-threatening arrhythmias (P=0.8009) between the two treatment groups. There was no significant difference in the percent of patients who stopped therapy because of an adverse event between the 2 treatment groups (overall 25%). There was, however, a significant difference in favor of amlodipine plus perindopril in the proportion of patients who stopped trial therapy because of a serious adverse events (2% vs 3%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			development of diabetes, development of renal impairment	
Cerebrovascular Disease				
PROGRESS[46] (2001) Perindopril 4 mg/day vs perindopril 4 mg/day and indapamide 2 to 2.5 mg/day vs placebo	DB, MC, PC, RCT Patients with a history of prior stroke or TIA within the previous 5 years	N=6,105 4 years	Primary: Fatal or nonfatal stroke Secondary: Fatal or disabling stroke, total major vascular events comprising the composite of nonfatal stroke, nonfatal myocardial infarction, or death due to any vascular cause (including unexplained sudden death); total and cause specific deaths; hospital admissions	Primary: Patients receiving active treatment experienced a 28% reduction in nonfatal or fatal stroke (95% CI, 17% to 38%; P<0.0001). There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (32% vs 27%; P<0.01) A trend towards a greater effect of active treatment among patients treated with combination therapy (43% risk reduction) than in those treated with single drug therapy (5% risk reduction) was reported. Secondary: There was a 33% reduction in fatal or disabling strokes in the active treatment group. Active treatment reduced the risk of total major vascular events by 26% (P=0.02). There were no significant differences between active treatment and placebo in total deaths from vascular or nonvascular causes. Among those assigned active treatment, there was a 9% RR reduction in hospitalization, with a median reduction of 2.5 days in the time spent in the hospital during follow-up. Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. Single drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.
Heart Failure				
Pfeffer et al.[53] (1992)	DB, MC, PC, RCT	N=2,231	Primary: Mortality from all	Primary: Mortality from all causes was significantly reduced in the captopril group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SAVE Captopril up to 50 mg TID vs placebo	Patients 21 to 80 years of age who had an acute myocardial infarction within 3-16 days and left ventricular dysfunction with an ejection fraction ≤40%, but without overt heart failure or symptoms of myocardial ischemia	42 months (average)	causes, mortality from cardiovascular causes, mortality combined with a decrease in EF ≥9 units, cardiovascular morbidity, combination of cardiovascular mortality and morbidity	(20%) vs placebo group (25%) for a 19% reduction in the risk of mortality from all causes (95% CI, 3% to 25%; P=0.019). The incidence of fatal cardiovascular events was consistently reduced in the captopril group with a 21% reduced risk of mortality from cardiovascular causes (P=0.014). The incidence of nonfatal major cardiovascular events was consistently reduced in the captopril group with a 25% reduced risk of recurrent myocardial infarction (P=0.015), 37% reduced risk for the development of severe heart failure (P<0.001), and 22% reduced risk of CHF requiring hospitalization (P=0.019). Long-term captopril administration was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events.
Pitt et al.[61] (1997) ELITE Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥65 years with symptomatic heart failure (NYHA class II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=722 1 year	Primary: Change in renal function Secondary: Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart failure, NYHA class, admission for myocardial infarction or unstable angina	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups). Secondary: Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, –4% to +55%; P=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% vs 8.7%; risk reduction, 46%; 95% CI, 5% to 69%; P=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to hospital for any reason was less frequent with losartan than with captopril treatment (22.2% vs 29.7%; P=0.014). More patients discontinued therapy due to adverse events with captopril (20.8%) than losartan (12.2%; P=0.002).
Pitt et al.[62] (2000)	DB, MC, PG, RCT Patients ≥60 years	N=3,152 555 days	Primary: All-cause mortality	Primary: No significant difference in all-cause mortality was reported between losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ELITE II Captopril 50 mg TID vs losartan 50 mg QD	old with symptomatic heart failure (NYHA II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	(mean follow-up)	Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	P=0.16). Secondary: Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI; 0.98 to 1.60; P=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7% vs 14.7%; P<0.001), including cough (0.3% vs 2.7%). Note: ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial, which reported a greater reduction in all-cause mortality with losartan compared with captopril.
Dickstein et al.[63] (2002) OPTIMAAL Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥50 years with an acute myocardial infarction and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18% vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; P=0.07). Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9% vs 7%; RR, 1.19; 95% CI, 0.98 to 1.43; P=0.07). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17% vs 23%; P<0.0001).
Pfeffer et al.[64] (2003) VALIANT Captopril 50 mg TID vs	DB, MC, RCT Patients ≥18 years of age with an acute myocardial infarction that was complicated by clinical or radiologic signs of heart failure and/or evidence of	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent myocardial infarction, hospitalization for	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (P=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (P=0.73). Secondary: The rate of death from cardiovascular causes, reinfarction, or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
valsartan 160 mg BID vs valsartan 80 mg BID and captopril 50 mg TID	left ventricular systolic dysfunction		heart failure	hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (P=0.20). The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (P=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.
CONSENSUS Trial Study Group[54] (1987) CONSENSUS Enalapril 2.5 to 40 mg per day vs placebo	DB, MC, PC, PG, RCT Patients with severe CHF (NYHA class IV symptoms), patients with recent myocardial infarction and unstable angina were excluded	N=253 188 days (average)	Primary: 6-month mortality and the cause of death Secondary: 12-month mortality and overall mortality	Primary: Mortality at 6 months was 26% and 44% for patients in the enalapril and placebo groups, respectively, for an overall reduction of 40% for enalapril (P=0.002). Secondary: At 12 months, enalapril reduced mortality by 31% compared to placebo (P=0.001). By the end of the study, there had been 50 deaths in the enalapril group and 68 deaths in the placebo group for a reduction of 27% (P=0.003). The entire reduction in total mortality was found to be among patients with progressive heart failure (a reduction of 50%), whereas no difference was seen in the incidence of sudden cardiac death. Note: The study was stopped early due to clear benefit with enalapril.
SOLVD Investigators[55] (1991) SOLVD Enalapril 2.5 to 20 mg per day	DB, MC, PC, RCT Patients with CHF and LVEF ≤35% receiving conventional therapy	N=2,569 41.4 months (average)	Primary: Mortality, rate of hospitalization for heart failure	Primary: Death was reported in 35.2% and 39.7% of patients receiving enalapril and placebo, respectively (risk reduction, 16%; 95% CI, 5% to 26%; P=0.0036). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (risk reduction, 22%; 95% CI, 6% to 35%). There was little apparent effect of treatment on deaths classified as due to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (risk reduction, 26%; 95% CI, 18% to 34%; P<0.0001).
SOLVD Investigators[56] (1992) SOLVD Enalapril 2.5 mg to 20 mg per day vs placebo	DB, MC, PC, RCT Patients 21 to 80 years of age with heart disease and an ejection fraction of ≤35% who were not receiving diuretics, digoxin or vasodilators for the treatment of heart failure	N=4,228 37.4 months (average)	Primary: All-cause mortality, incidence of heart failure, rate of hospitalization for heart failure	Primary: Enalapril resulted in an 8% reduction in risk for all-cause mortality (P=0.30). The difference was entirely due to a reduction in deaths due to cardiovascular causes, primarily progressive heart failure (risk reduction, 12%; P=0.12). In the placebo group, 30.2% of patients developed heart failure compared to 20.7% for enalapril (risk reduction, 37%; P<0.001). Rates of first hospitalization and multiple hospitalizations for CHF were higher with placebo (12.9% and 4.8%) than enalapril (8.7% and 2.7%; both P<0.001). The total number of deaths and cases of heart failure were lower in the enalapril group than in the placebo group (risk reduction, 29%; P<0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (risk reduction, 20%; P<0.001).
McKelvie et al.[65] (1999) RESOLVD Enalapril 10 mg BID vs candesartan 4 to 16 mg QD vs candesartan 4 to 8	DB, PG, MC, RCT Patients with CHF (NYHA classes II to IV), a 6 minute walk distance of 500 meters or less, and an ejection fraction <40%	N=768 43 weeks	Primary: Change in 6-minute walk distance Secondary: Change in NYHA functional class, quality of life, ejection fraction, ventricular volumes, neurohormone levels, safety	Primary: There were no significant differences among the groups with regards to the 6-minute walk distance over the 43-week study period. Secondary: There were no significant differences among the groups with regards to the NYHA functional class or quality of life at 18 or 43 weeks. Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (P=NS). End-diastolic volumes (P<0.01) and end-systolic volumes (P<0.05) increased less with combination therapy than with monotherapy with either agent. Aldosterone decreased with combination therapy at 17 but not 43 weeks compared with candesartan or enalapril (P<0.05). Brain natriuretic peptide

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD and enalapril 10 mg BID				decreased with combination therapy compared with candesartan and enalapril alone (P<0.01). Blood pressure decreased with combination therapy compared with candesartan or enalapril alone (P<0.05). Compared with enalapril, potassium decreased with candesartan use (P<0.05) and increased with candesartan plus enalapril (P<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality, or hospitalizations for CHF or any cause among the 3 groups.
Cohn et al.[66] (1991) V-HEFT II Enalapril 20 mg daily vs hydralazine 300 mg plus isosorbide dinitrate 160 mg daily	AC, DB, MC, RCT Men between the ages of 18 and 75 years with chronic heart failure receiving digoxin and diuretic therapy	N=804 2 years	Primary: Mortality Secondary: Peak oxygen consumption during exercise, LVEF	Primary: Mortality after 2 years was significantly lower in the group treated with enalapril (18%) than hydralazine plus isosorbide dinitrate (25%; P=0.016), and overall mortality tended to be lower (P=0.08). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (NYHA class I or II). Secondary: Peak oxygen consumption during exercise was increased only by hydralazine plus isosorbide dinitrate (P<0.05). While LVEF increased with both regimens during the 2 years after randomization, LVEF increased more (P<0.05) during the first 13 weeks in the hydralazine plus isosorbide dinitrate group.
Tu et al.[57] (2005) Enalapril vs lisinopril, ramipril, and other	RETRO Patients >65 years with newly diagnosed CHF initiated on ACE inhibitors who survived ≥30 days after hospital	N=6,753 ≤2 years	Primary: Combined end point of readmission for CHF as a primary diagnosis or mortality Secondary:	Primary: Relative to enalapril users, there were no significant differences in combined end point of readmission for CHF or mortality with lisinopril (AHR, 18; 95% CI, 0.94 to 1.23), ramipril (AHR, 16; 95% CI, 0.92 to 1.24) or other ACE inhibitors (AHR, 12; 95% CI, 0.90 to 1.17). Secondary: There were no significant differences among groups in readmission for CHF: enalapril 13% (AHR 1), lisinopril 15% (AHR, 1.11; 95% CI, 0.92 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ACE inhibitors (benazepril, captopril, cilazapril*, fosinopril, perindopril, quinapril and trandolapril)	discharge		CHF readmission alone and mortality alone	1.32), ramipril 15% (AHR, 1.19; 95% CI, 0.99 to 1.45), and other ACE inhibitors 15% (AHR, 1.13; 95% CI, 0.96 to 1.34). There were no significant differences among groups in mortality: enalapril 12% (AHR 1), lisinopril 13% (AHR, 19; 95% CI, 0.90 to 1.31), ramipril 12% (AHR, 0.97; 95% CI, 0.78 to 1.20), and other ACE inhibitors 11% (AHR, 0.94; 95% CI, 0.78 to 1.13).
Packer et al.[58] (1999) ATLAS Lisinopril 2.5 to 5 mg/day (low dose) vs lisinopril 32.5 to 35 mg/day (high dose)	DB, RCT Patients with NYHA class II, III, or IV symptoms of heart failure associated with a LVEF ≤30% despite treatment with diuretics for ≥2 months	N=3,164 39-58 months	Primary: All-cause mortality Secondary: cardiovascular mortality, hospitalizations (for any reason and for cardiovascular reasons), combinations of the primary and secondary end points	Primary: High-dose lisinopril was associated with a nonsignificant 8% lower risk of all-cause mortality compared to low-dose lisinopril (P=0.128). Secondary: Cardiovascular mortality was reported in 40.2% and 37.2% of patients receiving low-dose and high-dose lisinopril, respectively (P=0.073). High-dose lisinopril resulted in a 12% lower risk of death or hospitalizations for any reason (P=0.002), a 9% lower risk of cardiovascular mortality and hospitalization for cardiovascular reason (P=0.027) and 24% fewer hospitalizations for heart failure (P=0.002). Dizziness and renal insufficiency were observed more frequently in the high-dose group, but the 2 groups were similar in the number of patients requiring discontinuation of the study medication.
AIRE Study Investigators[59] (1993) AIRE Ramipril 2.5 to 5 mg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with acute myocardial infarction and clinical evidence of heart failure	N=2,006 15 months	Primary: All-cause mortality Secondary: First event in an individual patient (death, progression to severe or resistant heart failure, reinfarction, or stroke)	Primary: On the intention-to-treat analysis, all-cause mortality was significantly lower for patients randomized to receive ramipril (17%) than placebo (23%). The observed risk reduction was 27% (95% CI, 11% to 40%; P=0.002). Secondary: Analysis of prespecified secondary outcomes revealed a 19% risk reduction in the ramipril group compared to placebo (95% CI, 5% to 31%; P=0.008).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kober et al.[60] (1995) TRACE Trandolapril 1 to 4 mg QD vs placebo Medication was started between day 3 and 7 after the myocardial infarction.	DB, MC, PC, RCT Men and women >18 years who were hospitalized with a recent myocardial infarction and an LVEF ≤35%	N=1,749 24-50 months	Primary: Death from any cause Secondary: Death from a cardiovascular cause, sudden death, progression to severe heart failure (defined as the first of the following events: hospital admission for heart failure, death due to progressive heart failure, or heart failure necessitating the administration of open-label ACE inhibition), recurrent infarction, change in the wall-motion index	Primary: During the study, 34.7% of patients in the trandolapril group died compared with 42.3% in the placebo group (P=0.001). The relative risk of death in the trandolapril group was 0.78 compared to placebo (95% CI, 0.67 to 0.91). Secondary: Trandolapril reduced the risk of death from cardiovascular causes (RR, 0.75; 95% CI, 0.63 to 0.89; P=0.001) and sudden death (RR, 0.76; 95% CI, 0.59 to 0.98; P=0.03). Progression to severe heart failure was less frequent in the trandolapril group (RR, 0.71; 95% CI, 0.56 to 0.89; P=0.003). The risk of recurrent fatal or nonfatal myocardial infarction was not significantly reduced (RR, 0.86; 95% CI, 0.66 to 1.13; P=0.29). After three months, the mean change from the base-line index was 0.09 in the trandolapril group and 0.06 in the placebo group (P=0.03) but this statistically significant difference was absent at 6 and 12 months.
Hypertension				
Jamerson et al.[88] (2007) ACCOMPLISH Benazepril 20 to 40 mg QD and HCTZ 12.5 to 25 mg QD	DB, MC, RCT Patients >60 years of age with hypertension and at high risk of cardiovascular events n	N=10,704 Analysis performed at 6 months (complete trial duration 5 years)	Primary: Changes in mean SBP from baseline to 6 months, blood pressure control rates (SBP/DBP <140/90 mm Hg or <130/89 mm Hg for patients with	Primary: At baseline, 97% of subjects were treated with antihypertensive medications at entry, but only 37% of participants had blood pressure control. Mean blood pressure fell from 145/80 to 132/74 mm Hg after 6 months of treatment with either combination regimen (P<0.001). The 6-month blood pressure control rate was 73% in the overall trial (78%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD			diabetes and chronic kidney disease)	in the United States), 43% in diabetics and 40% in patients with renal disease. Of the patients uncontrolled, 61% were not on maximal medications.
Jamerson et al.[101] (2008) ACCOMPLISH Benazepril 20 to 40 mg QD and HCTZ 12.5 to 25 mg QD vs benazepril 20 to 40 mg QD and amlodipine 5 to 10 mg QD	DB, AC, MC, RCT Patients >60 years of age with hypertension and at high risk of cardiovascular events	N=11,506 36 months (mean)	Primary: The composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. Secondary: Death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke	Primary: There were 552 primary-outcome events in the benazepril+amlodipine group (9.6%) and 679 events in the benazepril+hydrochlorothiazide group (11.8%). The absolute risk reduction with benazepril+amlodipine therapy was 2.2% and the relative risk reduction was 19.6% compared to benazepril+hydrochlorothiazide (HR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). Secondary: For the secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, there were 288 (5%) events in the benazepril+amlodipine group compared to 364 (6.3%) events in the benazepril+hydrochlorothiazide group. The absolute risk reduction with benazepril+amlodipine therapy was 1.3% and the relative risk reduction was 21.2% compared to benazepril+hydrochlorothiazide (HR, 0.79; 95% CI, 0.67 to 0.92; P=0.002).
Malacco et al.[89] (2002) Captopril-HCTZ 50/25 mg/day (fixed-dose combination)	DB, MC, RCT Patients with mild-to-moderate arterial hypertension (sitting DBP >95 mm Hg and/or SBP >160	N=397 12 weeks	Primary: Reduction in sitting DBP and SBP Secondary: Percentage of	Primary: Significantly lower sitting DBP (–2.7 mm Hg; P<0.001) and SBP (–3.7 mm Hg; P<0.001) were achieved with amlodipine/benazepril compared to captopril/HCTZ. Secondary: Significantly more amlodipine/benazepril patients responded to therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amlodipine-benazepril 5/10 mg/day (fixed-dose combination)	mm Hg) inadequately controlled by monotherapy with an ACE inhibitor, calcium-channel blocking agent or diuretic		patients responding to therapy (DBP<90 mm Hg, reduction in DBP ≥10 mm Hg or SBP ≥20 mm Hg, or SBP <150 mm Hg)	(94.8%) compared to captopril/HCTZ (86.0%; P=0.004). No differences in adverse events were reported between the 2 treatment groups.
Elliot et al.[90] (1999) Enalapril 10 mg QD vs enalapril-felodipine ER 5/5 mg/day (fixed-dose combination) After 6 weeks, all patients received the fixed-dose combination for an additional 6 weeks.	DB, PG, PRO, RCT, XO Patients with sitting DBP >95 mm Hg and <115 mm Hg	N=217 12 weeks	Primary: Change in sitting DBP, proportion of responders (DBP <90 mm Hg or a reduction of >10 mm Hg	Primary: Patients receiving combination therapy had significantly greater reductions in sitting SBP and DBP compared with baseline (P<0.05 and P<0.01, respectively). More patients receiving combination therapy were classified as responders than patients receiving enalapril monotherapy (59% vs 41%; P<0.01). When patients originally taking 10 mg enalapril were crossed over to the combination therapy for an additional 6 weeks, there was a further blood pressure reduction and increase in response rate, with loss of significant differences compared with those treated continuously with the combination for the entire 12 weeks. There were no significant differences in tolerability between the regimens.
Estacio et al.[68] (1998) ABCD Enalapril 5 to 40 mg/day vs	DB, PRO, RCT Patients between the ages of 40 and 74 years with NIDDM, baseline DBP ≥90 mm Hg and receiving no antihypertensive medications at the	N=470 67 months	Primary: Effect of intensive (target DBP of 75 mm Hg) or moderate (target DBP between 80-89 mm Hg) blood-pressure control on the incidence and progression of	Primary: Analysis of the 470 patients in the trial who had hypertension (DBP ≥90 mm Hg) showed similar control of blood pressure, blood glucose and lipid concentrations between the 2 study medications throughout the 5 years of follow-up. Secondary: Nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarction than enalapril (RR, 7.0; 95% CI, 2.3 to 21.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nisoldipine 10 to 60 mg/day	time of randomization		complications of diabetes; compare enalapril to nisoldipine as a first-line antihypertensive agent Secondary: Incidence of myocardial infarction	
Wing et al.[69] (2003) ANBP2 Enalapril vs HCTZ The choice of the specific agent and dose was made by the family practitioner.	MC, OL, PRO, RCT Patients 65 to 84 years of age with average SBP while sitting of at least 160 mm Hg or an average DBP of at least 90 mm Hg (if the systolic blood pressure was at least 140 mm Hg)	N=6,083 4.1 years (median)	Primary: All cardiovascular events or death from any cause (both initial and subsequent fatal and nonfatal cardiovascular events)	Primary: By the end of the study, blood pressure had decreased to a similar extent in both groups (a decrease of 26/12 mm Hg). There were 695 cardiovascular events or deaths from any cause in the ACE inhibitor group (56.1 per 1,000 patient-years; HR, 0.89; 95% CI, 0.79 to 10; P=0.05) compared to 736 in the diuretic group (59.8 per 1,000 patient-years). The beneficial effects of ACE inhibitor treatment were more evident in male subjects (HR, 0.83; 95% CI, 0.71 to 0.97; P=0.02). The rates of nonfatal cardiovascular events and myocardial infarction decreased with ACE inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE inhibitor group).
Beckett et al.[71] (2008) HYVET Indapamide 1.5 mg/day vs	DB, MC, PC, RCT Patients ≥80 years (mean age 84 years) with sustained SBP ≥160 mm Hg	N=3,845 1.8 years (mean)	Primary: Fatal or nonfatal stroke Secondary: Death from any cause, death from cardiovascular causes, death from	Primary: At 2 years, 73.4% of patients in the active-treatment groups were receiving indapamide plus perindopril. Mean blood pressure while sitting was 15.0/6.1 mm Hg lower with active-treatment than placebo. Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, –1 to 51; P=0.06). Secondary:

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placebo Perindopril 2 to 4 mg/day or matching placebo was added to achieve BP <150/80 mm Hg.			stroke	Active treatment was associated with a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P=0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, –1 to 40; P=0.06) and a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P=0.05). Active treatment was associated with a 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001). Fewer serious adverse events were reported in the active-treatment group (358 vs 448; P=0.001).
ALLHAT[67] (2002) ALLHAT Lisinopril 10 to 40 mg/day vs amlodipine 2.5 to 10 mg/day vs chlorthalidone 12.5 to 25 mg/day Doses were titrated to achieve a goal blood pressure of <140/90 mm Hg.	DB, MC, RCT Patients ≥55 years with hypertension and at least 1 additional CHD risk factor	N=33,357 4.9 years (mean)	Primary: Combined fatal CHD or nonfatal myocardial infarction Secondary: All-cause mortality, fatal and nonfatal stroke, combined CHD, combined cardiovascular disease (combined CHD, stroke, treated angina without hospitalization, heart failure, and PAD)	Primary: There were no significant differences in the primary outcome between lisinopril (11.4%), amlodipine (11.3%) and chlorthalidone (11.5%). Secondary: All-cause mortality did not differ between groups. Five-year SBPs were significantly higher in the lisinopril (2 mm Hg; P<0.001) and amlodipine groups (0.8 mm Hg; P=0.03) compared to chlorthalidone, and 5-year DBPs were significantly lower with amlodipine (0.8 mm Hg; P<0.001). Amlodipine had a higher 6-year rate of heart failure compared to chlorthalidone (10.2% vs 7.7%; RR, 1.38; 95% CI, 1.25 to 1.52). Lisinopril had a higher 6-year rate of combined cardiovascular disease (33.3% vs 30.9%; RR, 1.10; 95% CI, 15 to 1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 12 to 1.30) and heart failure (8.7% vs 7.7%; RR, 1.19; 95% CI, 17 to 1.31).
Whelton et al.[70] (1990) Lisinopril 10 to 40	DB, MC, PG, RCT Patients with mild-to-moderate	N=70 Up to 8 weeks	Primary: Reduction in blood pressure in both ambulatory and	Primary: Lisinopril-treated patients showed significantly greater reductions in SBP and DBP measured by 24-hour ambulatory blood pressure monitoring compared with captopril-treated patients (P=0.023 and P=0.007,

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mg QD vs captopril 25 to 100 mg BID Doses were titrated until patients responded to treatment (defined by a decrease in office diastolic pressure to <90 mm Hg or at least a 10 mm Hg decrease from baseline).	essential hypertension		office settings	respectively). Greater reductions (P<0.05) were also noted in patients receiving lisinopril at hours 10 to 12, suggesting 2 blood pressure troughs for those receiving captopril. The difference in mean reductions between treatment groups from baseline to the final visit approached statistical significance for office SBP (P=0.06) and DBP (P=0.09) in favor of patients receiving lisinopril. Both drugs were well tolerated, and no patients withdrew form either treatment group.
Tytus et al.[72] (2007) Trandolapril 1 to 4 mg/day At 14 weeks after treatment initiation, subjects not achieving blood pressure targets could receive a combination of trandolapril 4 mg/day plus verapamil 240 mg/day with or without a diuretic.	MC, OL, PRO Patients with stage 1 or 2 hypertension who were treatment naïve (82%) or uncontrolled on a diuretic (11%) or calcium-channel blocker (7%); uncontrolled hypertension was defined as ≥140/90 mm Hg in subjects with no other risk factors or ≥130/80 mm Hg in subjects with diabetes or kidney disease	N=1,683 26 weeks	Primary: Percentage of patients reaching target blood pressure at 14 weeks Secondary: Percentages of subjects with stage 1 and 2 hypertension who achieved target blood pressure, percentages of subjects who achieved a drop in SBP of ≥20 mm Hg and/or DBP	Primary: At 14 weeks of treatment, 71.2% of patients who were treated with trandolapril monotherapy reached SBP/DBP <140/90 mm Hg. Secondary: At 26 weeks, 73.4% of patients achieved a target level of SBP/DBP <140/90 mm Hg. Of the 683 subjects with stage 2 hypertension, 64.6% achieved the target level after 14 weeks of trandolapril and 67.9% after 26 weeks. At 14 weeks, 78.8% of subjects treated with a trandolapril regimen experienced a decrease in SBP of ≥20 mm Hg or a decrease in DBP of ≥10 mm Hg. Statistically significant (P<0.001) and clinically relevant mean decreases in SBP of –16.1 mm Hg and in DBP of –8.8 mm Hg were observed from 4 weeks of treatment onward for the overall study population. The mean reductions in SBP and DBP were –21.5 and –11.9 mm Hg, respectively at 14 weeks (P<0.001), and –22.4 and –12.7 mm Hg, respectively, at 26

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			≥10 mm Hg, absolute changes in SBP and DBP, adverse events	weeks (P<0.001). A total of 343 predominantly mild, nonserious adverse events were attributed to the study drugs, reported by 15.3% of the 1,650 subjects. The most frequently reported nonserious adverse events were cough (6.3%); gastrointestinal disorders (2.3%), predominantly nausea; and headache (2.1%). No serious adverse events were attributed to the study treatment.
Pauly et al.[73] (1994) Trandolapril 4 mg QD vs captopril 50 mg BID If blood pressure was not normalized at 8 weeks, HCTZ 25 mg was added.	DB, MC, RCT Patients between 21 to 65 years with mild-to-moderate essential hypertension (DBP of 95-115 mm Hg)	N=180 16 weeks	Primary: Morning pre-dosing supine DBP at 8 weeks of monotherapy Secondary: Supine SBP at 8 weeks of monotherapy, blood pressure at 16 weeks of therapy (including 8 weeks of monotherapy and 8 weeks of combination therapy with HCTZ)	Primary: Significantly greater mean reductions in supine DBP in the trandolapril group vs captopril group were observed after 8 weeks of monotherapy (–13.5 vs –10.1 mm Hg; P=0.007). Secondary: Differences in supine SBP between treatment groups approached significance after 8 weeks of monotherapy (P=0.06). Both SBP and DBP were significantly reduced at all time points compared with baseline for both treatment groups at the end of the study (P<0.05). The proportion of patients whose blood pressure normalized (supine and standing blood pressure ≤160/90 mm Hg) at the end of the study was 61% for trandolapril and 44% for captopril (P=0.02). The overall proportion of responders (DBP fell by ≥10 or to <90 mm Hg) was significantly greater in the trandolapril group (77%) than in the captopril group (58%; P<0.007).
Vaur et al.[74] (1995) Trandolapril 2 mg QAM vs enalapril 20 mg Q AM	DB, RCT Patients between 18 to 70 years with mild-to-moderate primary hypertension	N=88 3 weeks	Primary: 24-hour ambulatory SBP and DBP over an active 24-hour period and subsequent 24-hour period (to mimic a missed dose)	Primary: Both trandolapril and enalapril showed similar reductions in SBP and DBP over the 24-hour period. In the trandolapril group, SBP and DBP decreased from 148/92 to 135/83 mm Hg (P<0.001). In the enalapril group, SBP and DBP decreased from 143/91 to 133/83 mm Hg (P<0.001). The trough/peak ratio on active treatment was 90% (SBP) and 54% (DBP) in the trandolapril group and 49% (SBP and DBP) in the enalapril group. Following the missed dose, trough/peak ratio decreased to 58% (SBP)/36% (DBP) for trandolapril and 10% (SBP)/19% (DBP) for enalapril. The blood pressure control was better sustained with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				trandolapril, such that significant falls in blood pressure were observed during the daytime, nighttime and early morning periods after a missed dose, whereas during the same periods, enalapril only significantly reduced blood pressure in the daytime period.
Karlberg et al.[94] (2000) Trandolapril 2 mg/day vs verapamil 240 mg/day vs trandolapril-verapamil 2/180 mg/day (fixed-dose combination)	DB, MC, PRO, RCT, XO Patients with uncomplicated primary hypertension (sitting DBP between 95 and 115 mm Hg) between the ages of 20-80 years	N=226 2 months	Primary: Change in blood pressure and rate pressure product Secondary: Predictive value of plasma concentrations of active renin regarding the blood pressure response to the different treatment regimens, safety	Primary: The mean fall in blood pressure was significantly greater with the combination (20/15 mm Hg; P<0.00054), as compared to both trandolapril (14/11 mm Hg) or verapamil (13/11) mm Hg. The difference between verapamil and trandolapril was not significant. Rate pressure product decreased significantly more on the combination (P<0.001) than on trandolapril or verapamil alone. Secondary: There was a significant positive correlation between blood pressure fall and plasma concentrations of active renin (e.g., the higher the initial active renin, the better the blood pressure response to trandolapril [P<0.045 for SBP and P<0.004 for DBP]). No relationships were found for either verapamil or the combination. All treatments were well tolerated and safe.
Pepine et al.[91] (2003) INVEST Verapamil SR 240 mg/day (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) vs	MC, OL, RCT Patients with essential hypertension	N=22,576 24 months	Primary: First occurrence of death (all cause), nonfatal myocardial infarction or stroke Secondary: cardiovascular death, angina, cardiovascular hospitalization, angina, blood pressure control (JNC VI goals SBP/DBP <140/90	Primary: At 24 months, in the calcium antagonist strategy (CAS) subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril and 43.7% HCTZ. In the non-calcium antagonist strategy (NCAS), 77.5% of patients were taking atenolol, 60.3% HCTZ and 52.4% trandolapril. After a follow-up of 61,835 patient-years (mean, 2.7 years per patient), 2,269 patients had a primary outcome event with no statistically significant difference between treatment strategies (9.93% in CAS vs 10.17% in NCAS; RR, 0.98; 95% CI, 0.90 to 16; P=0.57). Secondary: There was no significant difference in the rate of cardiovascular death (P=0.94) or cardiovascular hospitalization (P=0.59) between the 2 treatment groups.

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atenolol 50 mg/day (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.			mm Hg or <130/85 mm Hg if diabetic or renal impairment), safety	At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the CAS group (0.77 episodes/week) compared with the NCAS group (0.88 episodes/week; P=0.02). Two-year blood pressure control was similar between groups. The JNC VI blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of CAS patients and 64.0% (systolic) and 88.1% (diastolic) of NCAS patients. A total of 71.7% of CAS patients and 70.7% of NCAS patients achieved an SBP <140 mm Hg and DBP <90 mm Hg. Both regimens were generally well tolerated. Patients in the CAS group reported constipation and cough more frequently than patients in the NCAS group, while NCAS patients experienced more dyspnea, lightheadedness, symptomatic bradycardia and wheezing (all were statistically significant with P≤0.05).
Pepine et al.[92] (2006) INVEST Verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) vs atenolol (step 1), then add HCTZ if needed (step 2), then increase	MC, OL, RCT (Post hoc analysis of INVEST) Patients with essential hypertension	N=22,576 24 months	Primary: Risk for adverse outcome associated with baseline factors, follow-up blood pressure and drug treatments	Primary: Previous heart failure (adjusted HR, 1.96), as well as diabetes (HR, 1.77), increased age (HR, 1.63), United States residency (HR, 1.61), renal impairment (HR, 1.50), stroke/TIA (HR, 1.43), smoking (HR, 1.41), MI (HR, 1.34), peripheral vascular disease (HR, 1.27), and revascularization (HR, 1.15) predicted increased risk. Follow-up SBP <140 mm Hg (HR, 0.82) or DBP <90 mm Hg (HR, 0.70) and trandolapril with verapamil SR (HR, 0.78 and 0.79) were associated with reduced risk.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses of both (step 3), then add trandolapril (step 4)				
Brunner et al.[93] (2007) INVEST Verapamil SR 240 mg and trandolapril 1 to 4 mg	MC, OL, RCT (Post hoc analysis of INVEST) Patients with essential hypertension	N=1,832 24 months	Primary: Factors influencing blood pressure response to trandolapril add-on therapy	Primary: Trandolapril decreased mean unadjusted SBP and DBP by –9.1 and –4.1 mm Hg, respectively. The percentage of patients with blood pressure under control (<140/90 mm Hg) increased from 6.7% to 41.3% (P<0.0001). Adjusted blood pressure response was significantly associated with age and baseline SBP and DBP (P<0.0001). Whereas the decrease in SBP was more pronounced in younger patients, the opposite was observed for DBP decrease. DBP response was significantly associated with race. Specifically, the adjusted DBP decrease was significantly smaller in Hispanics and African Americans than whites (P=0.0032 and P=0.0069, respectively). However, Hispanics achieved a decrease in SBP and an increase in blood pressure control similar to the other ethnic groups.
Cifkova et al.[96] (2000) Verapamil-trandolapril 180/2 mg QD (VT) (fixed-dose combination) vs captopril-HCTZ 50/25 mg QD (CH) (fixed-dose combination) After 16 weeks,	AC, OL, RCT, XO Caucasian patients aged 18-75 years with mild-to-moderate essential hypertension (SBP 140-209 mm Hg and DBP 90-119 mm Hg)	N=100 8 months	Primary: LDL-C Secondary: Other lipid parameters (HDL-C, TC, triglycerides, apolipoproteins AI and B, lipoprotein(a)), blood pressure parameters	Primary: LDL-C was not significantly different between the 2 treatment groups (P=0.909). Secondary: All secondary lipid parameters remained unaltered except for HDL-C which was significantly higher with VT (1.39 vs 1.35 mmol/L; P<0.03). Serum potassium declined while uric acid and glucose increased on CH (all P<0.001). While there were no significant differences with respect to adjusted mean DBP, adjusted mean SBP was slightly higher on treatment with VT than with CH. These differences reached statistical significance for the 24-hour and night-time means, although the absolute adjusted mean treatment differences were only 2.3 mm Hg (P=0.02) and 3.5 mm Hg (P=0.01), respectively. The number of patients who achieved DBP <90 mm Hg at

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patients were switched to the other fixed combination for an additional 16 weeks.				the end of each treatment did not differ (56% VT vs 46% CH; P=NS). Heart rate was significantly lower in the VT group than the CH group (treatment differences ranged from 2.8-4.5 beats per minute; all P≤0.001).
Blood Pressure Lowering Treatment Trialists' Collaboration[75] (2007) ACE inhibitors (17 trials) vs ARBs (9 trials)	MA Patients with high blood pressure, diabetes, history or CHD or cerebrovascular disease	N=146,838 (26 trials) Variable duration	Primary: Nonfatal myocardial infarction or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease	Primary: From a total of 146,838 individuals with high blood pressure or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable blood pressure-dependent reductions in risk with ACE inhibitors and ARBs (P≥0.3 for all 3 outcomes). ACE inhibitors produced a blood pressure-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3 to 14%). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard (P=0.002). For both stroke and heart failure, there was no evidence of any blood pressure-independent effects of either ACE inhibitors or ARBs.
Diabetes/Diabetic Nephropathy/Renal Dysfunction				
Hou et al.[76] (2007) ROAD Benazepril 10 mg/day vs individual up-titration (10 to 40 mg/day with median dose of 20 mg/day) or losartan 50	OL, PRO, RCT Patients aged 18-70 years with proteinuria and chronic renal insufficiency who did not have diabetes	N=360 3.7 years (median follow-up)	Primary: Time to composite of doubling of serum creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	Primary: Compared with the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through up-titration were associated with a 51% and 53% reduction in the risk for the primary end point (P=0.028 and P=0.022, respectively). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages. Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable blood pressure control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared with their conventional dosages.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs individual up-titration (50 to 200 mg/day with median dose of 100 mg/day) Up-titration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.				There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages. Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (P>0.05). There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms.
Bakris et al.[87] (2008) GUARD Benazepril-HCTZ (fixed-dose combination) vs amlodipine-benazepril (fixed-dose combination) Doses were not specified.	DB, RCT Hypertensive, albuminuric type 2 diabetic patients, mean age 58 years were randomized to receive either initial fixed-dose combination product	N=322 52 weeks	Primary: Change in urinary albumin to creatinine ratio after 1 year of initial treatment with either fixed-dose combination, blood pressure reductions Secondary: Proportion who progressed to overt diabetic nephropathy, safety	Primary: Both combinations significantly reduced the urinary albumin to creatinine ratio compared to baseline (P<0.0001). The median percent change was –72.1% for benazepril/HCTZ and –40.5% for amlodipine/benazepril (P<0.0001). Both regimens significantly reduced SBP and DBP compared to baseline (P<0.0001). The mean reduction in both SBP and DBP was greater in the amlodipine-based arm than in the HCTZ-based arm; however, significance in favor of the amlodipine regimen was observed only for DBP (SBP –20.5 vs –18.8; P=0.19; DPB –13.1 vs –9.97; P=0.02). A greater proportion of patients who had microalbuminuria at baseline and treated with benazepril/HCTZ compared with amlodipine/benazepril attained normalization of the urinary albumin to creatinine ratio, defined as <30 mg/g (69.2% vs 47.8%; P=0.0004). Secondary: The percentage of patients progressing to overt proteinuria was similar for both groups. Overall, both study drugs were well tolerated. Adverse reactions possibly

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				related to the study medications occurred in 11.4% and 3.6% of patients receiving amlodipine/benazepril and benazepril/HCTZ, respectively. They included peripheral edema (7.8% vs 2.4%, respectively), fatigue (1.2% in each group), pitting edema (1.2% vs 0.0%), face edema (0.6% vs 0.0%) and thirst (0.6% vs 0.0%). More patients receiving the HCTZ-based regimen (10.8%) discontinued study drug than with the amlodipine-based regimen due to side effects (5.4%).
Barnett et al.[77] (2004) DETAIL Enalapril 20 mg/day vs telmisartan 80 mg/day	DB, MC, PG, RCT Patients aged 35 to 80 years with type 2 diabetes and hypertension	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; rates of ESRD and cardiovascular events; all-cause mortality	Primary: After 5 years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, –3.0 mL/min/1.73 m^2; 95% CI, –7.6 to 1.6). Therefore, the changes in GFR were comparable between the groups. Secondary: The effects of the 2 agents on the secondary end points were not significantly different after 5 years.
Mogensen et al.[78] (2000) CALM Lisinopril 20 mg QD vs candesartan 16 mg QD vs lisinopril 20 mg	DB, DD, MC, PG, RCT Patients 30 to 75 years old with hypertension, type 2 diabetes, and micro-albuminuria	N=199 24 weeks	Primary: Blood pressure and urinary albumin:creatinine ratio	Primary: At 12 weeks, mean reductions in DBP were 9.7 mm Hg (P<0.001) and 9.5 mm Hg (P<0.001), respectively, and in urinary albumin:creatinine ratio were 46% (P<0.001) and 30% (P<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (P<0.001) and 10.7 mm Hg for lisinopril alone (P<0.001). The reduction in urinary albumin:creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; P<0.001) and candesartan alone (24%; P=0.05). All treatments were generally well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD plus candesartan 16 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.				
DREAM Trial Investigators[79] (2006) DREAM Ramipril up to 15 mg/day vs placebo	DB, MC, PC, PRO, RCT, 2-by-2 factorial design Adults aged 30 years or more with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease	N=5,269 3 years (median)	Primary: Composite of newly diagnosed diabetes or death Secondary: Regression to normoglycemia, glucose levels, composite of cardiac and renal events (were not yet analyzed at the time of this publication)	Primary: The composite primary outcome did not differ significantly between the ramipril group (18.1%; HR, 0.91; 95% CI, 0.81 to 13; P=0.15) and the placebo group (19.5%). Secondary: Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (HR, 1.16; 95% CI, 17 to 1.27; P=0.001). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group than in the placebo group (P=0.07), though plasma glucose levels 2 hours after an oral glucose load were significantly lower in the ramipril group (P=0.01).
GISEN Group[80] (1997) REIN Ramipril 1.25 mg/day vs	DB, PC, RCT Patients between 18 and 70 years who were either normotensive (<140/90 mm Hg) or hypertensive with chronic nephropathy	N=166 16 months	Primary: Rate of GFR decline, extent to which this effect was dependent on the drug's antiproteinuric effect	Primary: Mean rate of GFR decline per month was significantly lower in the ramipril group than in the placebo group (0.53 mL/minute vs 0.88 mL/minute; P=0.03). Among the ramipril-assigned patients, percentage reduction in proteinuria was inversely correlated with decline in GFR (P=0.035) and predicted the reduction in risk of doubling of baseline creatinine or end-stage renal failure (18 ramipril vs 40 placebo; P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	and persistent proteinuria, who had not received ACE inhibition therapy for at least 2 months		Secondary: Blood pressure control, time to doubling of baseline serum creatinine or progression to end-stage renal failure, cardiovascular complications, total and cardiovascular mortality	Secondary: Blood pressure control and the overall number of cardiovascular events were similar in the 2 treatment groups. Fifty-eight patients (18 in the ramipril group and 40 in the placebo group) reached the combined end point of doubling of baseline serum creatinine concentration or end-stage renal failure (P=0.02). The risk of progression was still significantly reduced after adjustment for changes in SBP (P=0.04) and DBP (P=0.04) with ramipril, but not after adjustment for changes in proteinuria. Note: Originally, 352 patients were placed into stratum 1 (urinary protein excretion exceeding 1 g/24 hours) or stratum 2 (urinary protein excretion exceeding 3.0 g/24 hours). At the second planned interim analysis, the difference in decline in GFR between the ramipril and placebo groups in stratum 2 was highly significant (P=0.001). The Independent Adjudicating Panel therefore decided to open the randomization code and do the final analysis in this stratum while stratum 1 continued in the trial.
Wright et al.[81] (2002) AASK Ramipril 2.5 to 10 mg/day vs amlodipine 5 to 10 mg/day vs metoprolol 50 to 200 mg/day	DB, MC, RCT Patients were self-identified African Americans aged 18 to 70 years with hypertension and a GFR between 20 and 65 mL/minute/ 1.73 m^2 and no other identified cause of renal insufficiency	N=1,094 3-6.4 years	Primary: Rate of change in GFR (grouped by usual blood pressure [MAP goal 102 to 107 mm Hg] vs lower blood pressure [≤92 mm Hg]) Secondary: Clinical composite outcome (reduction in GFR by 50% or more, ESRD, or death)	Primary: No significant difference in primary outcome was reported between the usual blood pressure group compared with the lower blood pressure group (P=0.24). None of the drug group comparisons showed consistently significant differences in the GFR slope. Secondary: The lower blood pressure goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower blood pressure group, 2%; 95% CI, –22% to 21%; P=0.85). Ramipril resulted in significant risk reductions in the clinical composite outcomes compared with amlodipine (38%; 95% CI, 14% to 56%; P=0.004) and metoprolol (22%; 95% CI, 1% to 38%; P=0.04). There was no significant difference in the clinical composite outcome

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				between the amlodipine and metoprolol groups.
Bianchi et al.[105] (2010) Ramipril 10 mg and atorvastatin 10 mg QD (conventional therapy) vs spironolactone 25 mg, ramipril 10 mg, irbesartan 300 mg, and atorvastatin 10 mg QD (intensive therapy) The addition of diuretics, calcium antagonists, β-blockers or α1-receptor antagonists were added to achieve BP <130/80 mm Hg	RCT, OL Patients with a clinical diagnosis of idiopathic chronic glomerulonephritis (GN) and urine protein-creatinine ratio >1 g/g	N=128 36 months	Primary: Changes over time in proteinuria and eGFR Secondary: Adverse events and drop outs	Primary: Systolic BP decreased more in the intensive-therapy group (from 156.6 to 113.5 mm Hg) than in the conventional therapy group (from 155.7 to 122.7 mm Hg; P<0.01). Urine protein excretion decreased from 2.65 to 0.45 g/g creatinine with intensive therapy (P<0.001). With conventional therapy, urine protein excretion decreased from 2.60 to 1.23 g/g creatinine (P<0.001). With intensive therapy, eGFR did not significantly change over time (64.6 vs 62.9 mL/min/1.73 m^2). With conventional therapy, eGFR decreased from 62.5 to 55.8 mL/min/1.73 m^2 (P<0.01). Secondary: In the conventional therapy group, 8 patients discontinued the study due to hyperkalemia, cough, and rapid deterioration in kidney function. In the intensive therapy group, 15 dropped out due to hyperkalemia, cough, and hypotension. Nine patients in the intensive therapy group developed gynecomastia. Twelve patients on conventional and 31 on intensive therapy had to interrupt the study temporarily because of low BP. No patient developed an increase in creatine kinase, alanine aminotransferase, and alkaline phosphatase levels during the study.
Nakao et al.[82] (2003) COOPERATE Trandolapril 3 mg/day	DB, MC, PC, RCT Patients aged 18 to 70 years with chronic nephropathy (nondiabetic renal disease)	N=263 3 years	Primary: Composite of time to doubling of serum creatinine or ESRD Secondary: Changes in blood	Primary: The combined end point was reached in 11% of patients in the combination trandolapril and losartan group compared with 23% of patients in the trandolapril (P=0.018) and 23% of patients in the losartan group (P=0.016). Secondary: Mean SBP and DBP reductions were similar among the 3 treatment groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs losartan 100 mg/day vs trandolapril and losartan at equivalent doses			pressure, daily urinary protein excretion, adverse effects	(P=0.109). All patients receiving active treatment had significant decreases in urinary protein excretion, but the greatest difference was seen with the combination trandolapril and losartan group compared to trandolapril or losartan (–75.6%, –44.3% and –42.1%, respectively; P=0.01). The frequency of adverse events did not differ between groups, although a slightly higher occurrence of hyperkalemia and dry cough was recorded in the trandolapril and combination groups than in the losartan group.
Ruggenenti et al.[83] (2004) BENEDICT Trandolapril 2 mg/day vs verapamil SR 240 mg/day vs trandolapril 2 mg/day plus verapamil SR 180 mg/day (fixed-dose combination) vs placebo	DB, MC, RCT Patients ≥40 years with type 2 diabetes (not exceeding 25 years) and hypertension (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg) but with normo-albuminuria (urinary albumin excretion rate of <20 mcg/minute)	N=1,204 3.6 years (median)	Primary: Development of persistent microalbuminuria comparing combination therapy to placebo, acceleration factor Secondary: Primary end point comparing trandolapril and verapamil monotherapy to placebo, blood pressure, adverse events	Primary: The primary outcome was reached in 5.7% of patients receiving combination therapy versus 10.0% for patients receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01). Secondary: The primary outcome was reached in 6.0% of patients receiving trandolapril, 11.9% receiving verapamil and 10.0% receiving placebo. The estimated acceleration factor was 0.47 for trandolapril vs placebo (P=0.01) and 0.83 for verapamil vs placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Throughout the study the average trough SBP/DBP was 139/80 mm Hg for patients receiving trandolapril plus verapamil, 139/81 mm Hg for trandolapril, 141/82 mm Hg for verapamil and 142/83 mm Hg for placebo. The comparison was significant (P≤0.002) between trandolapril plus verapamil or trandolapril alone vs placebo, but not for verapamil vs placebo. Serious adverse events were similar in all treatment groups.
Casas et al.[84] (2005)	MA	127 studies	Primary: Doubling of serum	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ACE inhibitor or ARBs compared with placebo vs ACE inhibitor or ARBs compared with other antihypertensive drugs (β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) Specific agents and doses were not specified.	Studies in adults that examined the effect of any drug treatment with a blood-pressure lowering action on progression of renal disease	4.2 years (mean)	creatinine, and ESRD Secondary: Serum creatinine, urine albumin excretion and GFR	reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared with other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Strippoli et al.[85] (2004) ACE inhibitors vs placebo or ARBs vs	MA Patients with diabetic nephropathy	43 trials Duration at least 6 months, range 6-63.6 months	Primary: All-cause mortality, renal outcomes (ESRD, doubling of serum creatinine, microalbuminuria to macroalbuminuria)	Primary: ACE inhibitors significantly reduced all-cause mortality compared to placebo or no treatment (RR, 0.79; 95% CI, 0.63 to 0.99; P=0.04). There was a nonsignificant trend for reduction in ESRD (P=0.07) and doubling of serum creatinine (P=0.08) with ACE inhibitors compared to placebo or no treatment. ACE inhibitors significantly reduced the risk of progression from microalbuminuria to macroalbuminuria (P=0.0007) and increased regression back to normoalbuminuria (P<0.0001) compared to placebo or no treatment. ARBs did not significantly reduce all-cause mortality compared to placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17; P=0.95). ARBs significantly reduced the risk of ESRD (P=0.001) and doubling of serum creatinine (P=0.004). ARBs significantly decreased the risk of progression

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo or ACE inhibitors vs ARBs				to macroalbuminuria (P=0.001) and increased regression to normoalbuminuria (P=0.02) compared to placebo or no treatment. The 3 trials that compared ACE inhibitors to ARBs did not report on all-cause mortality, ESRD or doubling of serum creatinine. Progression from microalbuminuria to macroalbuminuria was reported in 1 trial (N=92) and there was no significant difference in risk, with the point estimate favoring ACE inhibitors (RR, 0.16; 95% CI, 0.02 to 1.44). Regression from microalbuminuria to normoalbuminuria in 1 trial showed a nonsignificant difference in the risk.
Strippoli et al.[86] (2006) ACE inhibitors vs placebo or ARBs vs placebo or ACE inhibitors vs ARBs	MA Patients with diabetic kidney disease	N=12,067 (49 trials) Duration at least 6 months	Primary: All-cause mortality, ESRD, doubling of serum creatinine concentration, progression from micro- to macroalbuminuria, regression from micro- to normoalbuminuria, drug-related toxicity (including cough, headache, hyperkalemia, impotence and pedal edema)	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No statistically significant reduction in the risk of all-cause mortality was found in the 3 studies that compared ACE inhibitors with ARBS (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of studies showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98) but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to 3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBS compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to 0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBS (RR, 0.68; 95% CI, 0.47 to 10 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively). ACE inhibitors and ARBS significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBS significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 15 to 1.93, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The 7 studies that compared ACE inhibitors to ARBS did not report the outcome of ESRD or doubling of serum creatinine. Progression from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in 1 trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBS. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBS were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment.
Miscellaneous				
Montalescot et al.[104] (2009) ARCHIPELAGO Enalapril 10 mg QD, followed by 20 mg QD on day 15 vs irbesartan 150 mg QD, followed by 300 mg QD on day 15	DB, AC, MC, RCT Adults with non-ST elevation acute coronary syndrome	N=429 60 days	Primary: Change from baseline in high-sensitivity C-reactive protein at day 60 Secondary: Changes in other inflammatory markers such as troponin I	Primary: High-sensitivity C-reactive protein levels were comparable in both treatment groups (irbesartan: 15.2 mg/L at baseline, 6.5 mg/L at day 60; absolute change of -8.7 mg/L; enalapril: 12.6 mg/L at baseline, 5.5 mg/L at day 60; absolute change of -7.1 mg/L, P=NS). Secondary: Similarly, mean levels of markers of myocardial injury (troponin I) and endothelial dysfunction (microalbuminuria) also decreased from baseline to day 60. with no significant differences between treatment groups.
Dagenais et al.[102] (2008) Ramipril 15 mg or rosiglitazone 8 mg QD	DB, PC, RCT Adults >30 years with impaired fasting glucose or impaired glucose tolerance without	N=5,269 3 years	Primary: Composite cardiorenal outcome (first occurrence of any cardiovascular death, nonfatal MI,	Primary: Compared with placebo, neither ramipril (15.7% vs 16.0%; HR, 0.98; P=0.75) nor rosiglitazone (15.0% vs 16.8%; HR, 0.87; P=0.07) reduced the risk of the cardiorenal composite outcome. Secondary: Ramipril had no impact on the CVD and renal components. Rosiglitazone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	known CVD or renal insufficiency		stroke, new heart failure, progression to microalbuminuria or proteinuria, renal insufficiency requiring dialysis or transplantation) Secondary: Subcomponents of the primary analysis	increased heart failure (0.53 vs 0.08%; HR, 7.04; P=0.01), but reduced the risk of the renal component (HR, 0.80; P=0.005).
Belluzzi et al.[103] (2009) Ramipril 5mg QD vs placebo	DB, PC, RCT Adults with lone atrial fibrillation without heart disease or hypertension	N=62 3 years	Primary: Relapse of atrial fibrillation as determined by clinical assessment, ECG, 24 hour Holter monitor, and questionnaire collection.	Primary: At the end of the study, atrial fibrillation relapses were observed in 3 ramipril-treated patients and in 10 control patients (P<0.03).
Hansson et al.[106] (1998) HOT Aspirin 75 mg QD vs placebo A five step antihypertensive treatment	MC, RCT, OL Adults with hypertension and a DBP between 100 and 115 mm Hg	N=18,790 3.8 years	Primary: Major cardiovascular events (fatal and nonfatal, fatal and nonfatal stroke, and all other cardiovascular deaths)	Primary: There were 9.9, 10.0, and 9.3 major cardiovascular events per 1000-patients years, respectively, in the DBP ≤90, DBP ≤85, and DBP ≤80 treatment groups (P=0.50), thus suggesting that the reduction of DBP below 90 mm Hg does not provide any mortality or morbidity advantage. Aspirin reduced major cardiovascular events by 15% (P=0.03) and all myocardial infarction by 36% (P=0.002), with no effect on stroke. There were seven fatal bleeds in the aspirin group and eight in the placebo group, and 129 versus 70 non-fatal major bleeds in the two groups, respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
regimen: 1) felodipine 5 mg QD, 2) ACE inhibitor or β-blocker, 3) dose titrations, 4) dose titrations, 5) diuretic.				

*Product not available in the United States
Drug regimen abbreviations: BID=twice daily, Q AM=every morning, QD=once daily, SR=sustained-release, TID=three times daily
Study abbreviations: AC=active comparator, AHR=adjusted hazard ratio, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ARB=angiotensin II receptor antagonist, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, DBP=diastolic blood pressure, ECG=electrocardiogram, ESRD=end-stage renal disease, GFR=glomerular filtration rate, HDL-C=high-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MAP=mean arterial pressure, NIDDM=non-insulin dependent diabetes mellitus, NYHA=New York Heart Association, PCI=percutaneous coronary intervention, PVD=peripheral vascular disease, SBP=systolic blood pressure, TIA=transient ischemic attack

Additional Evidence

Dose Simplification
Taylor et al. evaluated adherence rates with amlodipine/benazepril fixed-dose combination compared to an ACE inhibitor + long-acting dihydropyridine administered as separate formulations.[99] There was no significant difference in adherence in younger subjects (18-39 year olds); however, in all age group combined, adherence rates were higher with amlodipine/benazepril compared to the use of an ACE inhibitor + a long-acting dihydropyridine (80.8% vs 73.8%; P<0.001). Dickson et al. evaluated adherence rates with amlodipine/benazepril fixed-dose combination compared to an ACE inhibitor + long-acting dihydropyridine administered as separate formulations in an elderly Medicaid population.[98] Over a 12 month period, adherence rates were reported to be significantly higher with fixed-dose combination product compared to the administration of an ACE inhibitor and dihydropyridine as separate formulations (63.4% vs 49.0%; P<0.0001). Dezzi et al. also reported significantly higher compliance rates at 12 months in patients receiving fixed-dose lisinopril/hydrochlorothiazide (68.7%) or enalapril/hydrochlorothiazide (70.0%) versus administration of the components as separate formulations (57.8% and 57.5%, respectively; P<0.05 for both comparisons).[97]

Stable Therapy
Sapienza et al. evaluated the impact of converting long-term care patients from high-dose calcium-channel blockers or ACE inhibitor + calcium-channel blockers to a fixed-dose combination of amlodipine/benazepril.[95] There was no significant change in blood pressure from baseline following the conversion; however, there was a significant reduction (81.8%) in the number of patients reporting ≥1 drug-related adverse event (22 vs 4; P<0.05), particularly edema (75% reduction).

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 12. Relative Cost of the Angiotensin-Converting Enzyme Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Benazepril	tablet	Lotensin®*	$$	$
Benazepril and hydrochlorothiazide	tablet	Lotensin HCT®*	$$	$
Captopril	tablet	N/A	N/A	$
Captopril and hydrochlorothiazide	tablet	N/A	N/A	$
Enalapril	tablet	Vasotec®*	$$$-$$$$	$
Enalapril and hydrochlorothiazide	tablet	Vaseretic®*	$$-$$$	$-$$
Fosinopril	tablet	Monopril®*	$$$	$
Fosinopril and hydrochlorothiazide	tablet	N/A	N/A	$$
Lisinopril	tablet	Prinivil®*, Zestril®*	$$$	$
Lisinopril and hydrochlorothiazide	tablet	Prinzide®*, Zestoretic®*	$$-$$$	$
Moexipril	tablet	Univasc®*	$$$	$$
Moexipril and hydrochlorothiazide	tablet	Uniretic®*	$$$	$$
Perindopril	tablet	Aceon®*	$$$	$
Quinapril	tablet	Accupril®*	$$	$
Quinapril and hydrochlorothiazide	tablet	Accuretic®*	$$	$$
Ramipril	capsule, tablet	Altace®*	$$$	$
Trandolapril	tablet	Mavik®*	$	$
Trandolapril and verapamil	extended-release tablet	Tarka®*	$$-$$$	$$$-$$$$

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

X. Conclusions

All of the angiotensin-converting enzyme (ACE) inhibitors are approved for the treatment of hypertension.[1-20] Some of the products are also approved for the treatment of diabetic nephropathy, heart failure and post-myocardial infarction. The ACE inhibitors are available as single entity products, as well as in combination with hydrochlorothiazide or verapamil. All of the products are available in a generic formulation.

There are numerous national and international guidelines that recommend the use of ACE inhibitors in patients with the following conditions: acute coronary syndrome, cerebrovascular disease, coronary artery disease, diabetes, diabetic nephropathy, heart failure, hypertension, left ventricular dysfunction, left ventricular hypertrophy, previous myocardial infarction and renal disease.[25-42] In general, guidelines do not give preference to one ACE inhibitor over another.

In clinical trials, the ACE inhibitors have been shown to reduce cardiovascular morbidity and mortality, preserve renal function in patients with nephropathy, and effectively lower blood pressure when administered as monotherapy or in combination with other antihypertensive agents.[44-47,53-56,59-60,66,69,72,76-78,80-87,90,94] Most patients will need more than one antihypertensive agent to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[35,97-99,107] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

There is insufficient evidence to support that one brand angiotensin-converting enzyme 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 angiotensin-converting enzyme 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 angiotensin-converting enzyme 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 Angiotensin II Receptor Antagonists
AHFS Class 243208
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I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[19-20] Excessive activity of the RAAS may lead to hypertension, as well as fluid and electrolyte disorders.[21] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase).[19] Angiotensin II can increase blood pressure by direct vasoconstriction, as well as through actions on the brain and autonomic nervous system.[19,21] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental effects, including ventricular hypertrophy, remodeling and myocyte apoptosis.[19-20]

The angiotensin II receptor antagonists are approved for the treatment of diabetic nephropathy, heart failure, hypertension and post-myocardial infarction.[1-18] Since angiotensin II may be generated through other pathways that do not depend upon ACE, blockade of angiotensin II by ACE inhibitors is incomplete.[19-20] Angiotensin II receptor antagonists block the angiotensin II receptor subtype AT_1, preventing the negative effects of angiotensin II, regardless of its origin. They do not appear to affect bradykinin and may be an option for patients who cannot tolerate ACE inhibitors. All of the angiotensin II receptor antagonists are available as single entity products, as well as in combination with hydrochlorothiazide. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride. Telmisartan is also available in combination with amlodipine, which is a potent vasodilator.

The angiotensin II receptor antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Losartan and losartan/hydrochlorothiazide are available in a generic formulation. Tribenzor® (olmesartan, amlodipine and hydrochlorothiazide) is a fixed-dose combination product that was added to Medicaid's drug file in August 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 September 2008.

Table 1. Angiotensin II Receptor Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Candesartan	tablet	Atacand®	none
Candesartan and hydrochlorothiazide	tablet	Atacand HCT®	none
Eprosartan	tablet	Teveten®	Teveten®
Eprosartan and hydrochlorothiazide	tablet	Teveten HCT®	Teveten HCT®
Irbesartan	tablet	Avapro®	Avapro®
Irbesartan and hydrochlorothiazide	tablet	Avalide®	Avalide®
Losartan	tablet	Cozaar®*	losartan
Losartan and hydrochlorothiazide	tablet	Hyzaar®*	losartan and hydrochlorothiazide
Olmesartan	tablet	Benicar®	Benicar®
Olmesartan and hydrochlorothiazide	tablet	Benicar HCT®	Benicar HCT®
Telmisartan	tablet	Micardis®	Micardis®
Telmisartan and amlodipine	tablet	Twynsta®	none
Telmisartan and hydrochlorothiazide	tablet	Micardis HCT®	Micardis HCT®
Valsartan	tablet	Diovan®	Diovan®
Valsartan and hydrochlorothiazide	tablet	Diovan HCT®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the angiotensin II receptor antagonists are summarized in Table 2. For a more comprehensive overview of the pharmacologic treatment of acute myocardial infarction, angina pectoris, heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Angiotensin II Receptor Antagonists

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation**[40] **(2008)**	Prophylactic Therapies in the Acute Phase • At discharge and in the absence of contraindications, all patients should be treated with ASA, a thienopyridine, a β-blocker and a statin. In patients with significant LV dysfunction, an ACE inhibitor (or an ARB) should be added. With the exception of the thienopyridine, these medications should be given indefinitely. Secondary Prevention • ACE inhibitor in all patients without contraindications, regardless of blood pressure or LV function. • Angiotensin receptor blockers in all patients without contraindications who do not tolerate ACE inhibitors, regardless of blood pressure or LV function.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI)**[38] **(2007)**	Secondary Prevention • For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with β-blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure. • Use of angiotensin receptor blockers is recommended in patients who are intolerant of ACE inhibitors and have HF or have had an MI with LVEF ≤40%. • It is beneficial to use angiotensin receptor blocker therapy in other patients who are ACE inhibitor intolerant and have hypertension. • Considering use of angiotensin receptor blockers in combination with ACE inhibitors in systolic dysfunction HF may be reasonable.
National Institute for Health and Clinical Excellence (NICE): **Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction**[39] **(2007)**	Secondary Prevention • Routine use of angiotensin receptor blockers after an acute MI is not recommended. • Angiotensin receptor blockers are recommended in patients who are intolerant to ACE inhibitor therapy. • Combination therapy with an ACE inhibitor and an angiotensin receptor blocker is not routinely recommended in patients early after an acute MI with heart failure and/or left ventricular systolic dysfunction.
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**[23] **(2007)**	• Angiotensin receptor blockers are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a left ventricular ejection fraction of ≤40%. • Angiotensin receptor blockers may be considered in combination with an ACE inhibitor due to left ventricular systolic dysfunction.
European Society of Cardiology (ESC): **Management of Stable Angina Pectoris**[25] **(2006)**	• The role of angiotensin receptor blockers is not addressed in this guideline.

Clinical Guideline	Recommendation(s)
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease**[27] **(2004)**	• The role of angiotensin receptor blockers is not addressed in this guideline.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)**[24] **(2007)**	Early Hospital Care • An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of HF or LVEF ≤40%. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge • Angiotensin receptor blockers should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and signs of heart failure and left ventricular ejection fraction <40%. • Combination ACE inhibitor and angiotensin receptor blocker therapy may be considered in patients with persistent symptomatic heart failure and left ventricular ejection fraction <40% despite conventional therapy including an ACE inhibitor or angiotensin receptor blocker alone.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)**[26] **(2007)**	Long-term Management • Angiotensin receptor blockers should be considered in patients intolerant to ACE inhibitors and/or who have heart failure or have had an MI with a left ventricular ejection fraction of ≤40%.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline**[29] **(2010)**	Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction • ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema. • Routine use of the combination of ACE inhibitors and ARBs for prevention of heart failure is not recommended. Patients With Left Ventricular Systolic Dysfunction • ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. • ARBs are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. • ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. • Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with heart failure post-MI or chronic heart failure and reduced LVEF. • The routine use of an ARB is not recommended in addition to ACE inhibitor and β-blocker therapy in patients with a recent acute MI and reduced LVEF. • The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE

Clinical Guideline	Recommendation(s)
	inhibitor and β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • In the absence of other specific indications for these drugs, ARBs or ACE inhibitors may be considered in patients with heart failure and preserved LVEF. • ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. In patients who meet these criteria but are intolerant to ACE inhibitors, ARBs should be considered. Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended. Managing Heart Failure in Special Population • ACE inhibitor and β-blocker therapy are recommended in all women with symptomatic or asymptomatic heart failure and LV systolic dysfunction. ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency. • ACE inhibitor and β-blocker therapy are recommended in all African American patients with symptomatic or asymptomatic heart failure and LV systolic dysfunction. ARBs are recommended as substitute therapy for heart failure in African Americans intolerant of ACE inhibitors.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults[28] (2009)**	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors, and β-blockers have been shown to prevent heart failure. The ARBs losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes mellitus and nephropathy. • ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction, and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension. • ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes, and hypertension with other cardiovascular risk factors. Patients With Cardiac Structural Abnormalities or Remodeling Who Have not Developed Heart Failure Symptoms (Stage B) • ARBs are recommended for patients with reduced left ventricular ejection fraction and a history of an MI if they are intolerant to ACE inhibitors. • ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy. • ARBs can be beneficial in patients with low EF and no symptoms of

Clinical Guideline	Recommendation(s)
	HF who are intolerant of ACEIs. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • ARBs are recommended in patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction who are intolerant to ACE inhibitors. • ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced left ventricular ejection fraction. • The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment. • The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • β-blockers, ARBs, ACE inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms. Hospitalized Patients • Oral therapies known to improve outcomes (ACE inhibitors, ARBs, β-blockers) should be continued during hospitalization. If not currently treated with these therapies, initiation is recommended prior to hospital discharge.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[30] (2008)**	Pharmacologic Therapy of Chronic Heart Failure • ARBs are recommended in patients with heart failure and LVEF ≤40% as an alternative in patients with mild to severe symptoms (NYHA class II–IV) who are intolerant of an ACE inhibitor or in patients with persistent symptoms (NYHA class II–IV) despite treatment with an ACE inhibitor and β-blocker. Comorbidities and Special Populations • Antihypertensive regimens based on renin–angiotensin system antagonists (ACE inhibitors or ARBs) are preferable. • In hypertensive patients with HFPEF, aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended. ACE inhibitors and/or ARBs should be considered the first-line agents. • ACE inhibitors and ARBs can be useful in patients with diabetes mellitus to decrease the risk of end-organ damage and cardiovascular complications and subsequently risk of heart failure. • Agents with documented effects on morbidity and mortality such as ACE inhibitors, β-blockers, and ARBs are recommended in patients with co-existing pulmonary disease.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management[107] (2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the

Clinical Guideline	Recommendation(s)
	initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • Several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an ARB or a CCB, and in recent large-scale trials for the ACE inhibitor/CCB combination. The ARB/CCB combination also appears to be rational and effective. These combinations can be recommended for priority use. • Use of an ACE inhibitor/ARB combination may increase adverse events. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment. • Combination treatment is commonly needed to effectively lower blood pressure in diabetic patients. A renin–angiotensin receptor blocker should always be included because of the evidence of its protective effect against initiation or progression of nephropathy.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[33] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. • The choice of drug should depend on several factors, including previous patient response to a class of medications, the effect of a medication on cardiovascular risk according to the patient's cardiovascular profile, presence of compelling indications for certain medications, the presence of disorders which may limit the use of a class of medications, possibility of drug interactions, and side effects. • Drugs which exert their effects for 24 hours and can be given once daily should be preferred to enhance compliance. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors, ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end-stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.

Clinical Guideline	Recommendation(s)
	• CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, and the combination is likely to be well tolerated.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[34] (2006)**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • Initial therapy in patients younger than 55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[31] (2004)**	• Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • In patients with acute coronary syndromes (myocardial infarction or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. • For patients with post-myocardial infarction, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients

Clinical Guideline	Recommendation(s)
	with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2 to 4 times higher in African American patients. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant. • ACE inhibitors should not be used in patients who have a history of angioedema.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[37] (2004)**	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-myocardial infarction with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-myocardial infarction (β-blockers), chronic stable angina (CCBs, β-blockers), high CAD risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), and supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension[32] (2003)**	• When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics, dihydropyridine CCBs), renal disease (ACE inhibitors, ARBs), post-myocardial infarction (ACE inhibitors, β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics, ACE inhibitors). • If combination therapy is required, a diuretic should generally be a

Clinical Guideline	Recommendation(s)
	component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[36] **(2003)**	• All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required. • ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy. • CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients. • African American patients appear to be at an increased risk for ACE inhibitor-associated cough, angioedema, or both. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[35] **(2010)**	<u>Hypertension</u> • Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥30 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <30 mL/min/1.73 m^2. <u>Diabetic Nephropathy</u> • In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used. • In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. • In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. • In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy. • If one class is not tolerated, the other should be substituted.

III. Indications

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

Table 3. FDA-Approved Indications for the Angiotensin II Receptor Antagonists (Drugs C – L)[1-18]

Indication	Candesartan	Candesartan/ HCTZ	Eprosartan	Eprosartan/ HCTZ	Irbesartan	Irbesartan/ HCTZ	Losartan	Losartan/ HCTZ
Cerebrovascular Risk Reduction								
To reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients.							✔	✔
Heart Failure								
Treatment of heart failure (NYHA class II to IV and ejection fraction up to 40%) to reduce the risk of death from cardiovascular causes and reduce hospitalizations for heart failure	✔							
Hypertension								
Treatment of hypertension	✔ *	✔ †	✔ *	✔ *†	✔ *	✔	✔ *	✔ ††
Nephropathy in Type 2 Diabetic Patients								
Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension to reduce the rate of progression of nephropathy					✔		✔	

*Alone or in combination with other antihypertensive agents.
†This fixed combination drug is not indicated for the initial therapy of hypertension.
††This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

Table 4. FDA-Approved Indications for the Angiotensin II Receptor Antagonists (Drugs O – V)[1-18]

Indication	Olmesartan	Olmesartan/ HCTZ	Telmisartan	Telmisartan/ Amlodipine	Telmisartan/ HCTZ	Valsartan	Valsartan/ HCTZ
Cardiovascular Risk Reduction							
Reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients ≥55 years of age at high risk of developing major cardiovascular events who are unable to take ACE inhibitors			✔				
Heart Failure							
Treatment of heart failure (NYHA class II-IV) to significantly reduce hospitalizations for heart failure						✔	
Hypertension							
Treatment of hypertension	✔ *	✔ †	✔ *	✔ *	✔ †	✔ *	✔
Myocardial Infarction							
To reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction						✔	

*Alone or in combination with other antihypertensive agents.
†This fixed combination drug is not indicated for the initial therapy of hypertension.

IV. Pharmacokinetics

The pharmacokinetic parameters of the angiotensin II receptor antagonists are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Angiotensin II Receptor Antagonists[1-18]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Candesartan	15	>99	Intestinal wall (>99)	Renal (33) Feces (67)	9
Eprosartan	13	98	Liver (20)	Renal (7) Feces (90)	5-9
Irbesartan	60-80	90	Liver (50-70)	Renal (20) Feces (65)	11-15
Losartan	25-35	99	Liver (14)	Renal (13-35) Feces (50-60)	2
Olmesartan	26	99	Intestinal wall (100)	Renal (35-50) Feces (50-65)	13
Telmisartan	42-58	>99	Liver (<3)	Feces (97)	24
Valsartan	25	95	Liver, minimal	Renal (7-13) Feces (83)	6-9
Amlodipine	60-65	93-98	Liver, extensive	Renal (60) Feces (20-25)	35-50
Hydrochlorothiazide	50-75	40-68	Not metabolized	Renal (50-70)	6-15

V. Drug Interactions

Significant drug interactions with the angiotensin II receptor antagonists are listed in Table 6.

Table 6. Significant Drug Interactions with the Angiotensin II Receptor Antagonists[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Angiotensin II receptor antagonists (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)	1	Potassium-sparing diuretics	Angiotensin II receptor antagonists and potassium-sparing diuretics may increase serum potassium levels, leading to additive or synergistic effects.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Hydrochlorothiazide	1	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has occurred.
Amlodipine	2	HIV protease inhibitors	Pharmacologic effects of amlodipine may be enhanced by protease inhibitors.
Amlodipine	2	Imidazoles	Imidazoles may increase the plasma concentrations and pharmacologic effects of amlodipine.
Angiotensin II receptor	2	ACE Inhibitors	Coadministration of angiotensin

Generic Name(s)	Significance Level	Interaction	Mechanism
antagonists (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)			II receptor antagonists and ACE inhibitors may be associated with an increased risk of renal dysfunction and/or hyperkalemia.
Angiotensin II receptor antagonists (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)	2	Lithium	Angiotensin II receptor antagonists may decrease lithium renal excretion by enhancing its reabsorption. Lithium levels may increase, resulting in an increase in pharmacologic and toxic effects of lithium.
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided.
Hydrochlorothiazide	2	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the angiotensin II receptor antagonists are listed in Table 7. The most common adverse drug events reported with amlodipine and hydrochlorothiazide are listed in Table 8. The boxed warning for the angiotensin II receptor antagonists is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Combination Angiotensin II Receptor Antagonists[1-18]

Adverse Events	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Cardiovascular							
Chest pain	>1	≥1	≥1	≥1	>0.5	1	-
Hypertension	-	-	<1	-	-	-	-
Hypotension	-	<1	<1	<1	-	-	<1
Orthostatic hypotension	-	✔	✔	-	-	-	-
Tachycardia	≥0.5	<1	≥1	<1	>0.5	>0.3	-
Central Nervous System							
Anxiety/nervousness	≥0.5	<1	≥1	<1	-	>0.3	>0.2
Depression	≥0.5	1	<1	<1	-	>0.3	-
Dizziness	4	≥1	≥1	4	3	1	>1
Fatigue	>1	2	4	-	>0.5	1	2
Headache	≥1	≥1	≥1	≥1	>1	1	>1
Insomnia	-	<1	-	1	>0.5	>0.3	>0.2
Dermatological							
Rash	≥0.5	<1	≥1	<1	>0.5	>0.3	>0.2
Gastrointestinal							
Abdominal pain	>1	2	≥1	≥1	>0.5	1	2
Diarrhea	>1	≥1	3	2	>1	3	>1
Dyspepsia/heartburn	≥0.5	≥1	2	1	>0.5	1	>0.2
Nausea/vomiting	>1	<1	≥1	≥1	>0.5	1	>1
Genitourinary							
Albuminuria	>1	<1	-	-	-	-	-
Hematuria	≥0.5	<1	-	-	>1	-	-
Urinary tract infection	-	4	≥1	<1	>0.5	1	-
Laboratory Test Abnormalities							
Creatine phosphokinase increased	≥0.5	<1	-	-	>1	-	-
Hyperglycemia	≥0.5	<1	-	-	>1	-	-
Hyperkalemia	✔	-	✔	✔	-	-	✔
Hypertriglyceridemia	≥0.5	1	-	-	>1	-	-
Hypokalemia	-	✔	-	-	-	-	-
Musculoskeletal							
Arthralgia	>1	2	-	<1	>0.5	>0.3	>1

Adverse Events	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Muscle cramp	-	-	-	1.1	-	-	>0.2
Myalgia	≥0.5	≥1	-	1	>0.5	1	>0.2
Pain (includes back and leg)	3	<1	≥1	1-2	>1	1-3	>0.2
Trauma	-	-	2	-	-	-	-
Respiratory							
Bronchitis	>1	≥1	-	<1	>1	>0.3	-
Cough	>1	4	3	3	-	1	>1
Influenza/influenza-like symptoms	-	<1	≥1	<1	>1	1	-
Nasal congestion	-	-	-	2	-	-	-
Pharyngitis	2	4	≥1	≥1	>1	1	>1
Rhinitis	2	4	≥1	<1	>1	>0.3	>1
Sinus disorder	-	-	≥1	2	-	-	-
Sinusitis	>1	≥1	-	1	>1	3	>1
Upper respiratory tract infection	6	8	9	8	>1	7	>1
Miscellaneous							
Allergic reactions	✔	✔	✔	✔	✔	✔	✔
Angioedema	✔	✔	✔	✔	✔	✔	✔
Edema	>1	≥1	≥1	≥1	>0.5	1	>1
Inflicted injury	-	2	-	-	>1	-	-
Viral infection	-	2	-	-	-	-	3

✔ Percent not specified
- Event not reported

Table 8. Adverse Drug Events (%) Reported with Amlodipine and Hydrochlorothiazide[1-18]

Adverse Events	Amlodipine	Hydrochlorothiazide
Cardiovascular		
Edema	2-11	-
Hypotension	-	1-10
Orthostatic hypotension	-	1-10
Palpitations	1-5	-
Peripheral ischemia	1	-
Peripheral edema	18-26	-
Vasculitis	1	-
Ventricular tachycardia	1	-
Central Nervous System		
Abnormal dreams	1	-
Agitation	1	-
Amnesia	1	-
Apathy	1	-
Depersonalization	1	-
Dizziness	1	-
Headache	7	-
Nervousness	1	-
Peripheral neuropathy	1	-
Somnolence	<2	-
Vertigo	1	-
Dermatologic		
Alopecia	-	<1
Cold and clammy skin	1	-
Erythema multiforme	1	<1
Exfoliative dermatitis	-	<1
Flushing	1-3	-
Photosensitivity	-	1-10
Pruritus	1	-
Skin discoloration	1	-
Skin dryness	1	-
Stevens-Johnson syndrome	-	<1
Urticaria	1	-
Toxic epidermal necrolysis	-	<1
Endocrine and Metabolic		
Gynecomastia	✔	-
Thirst	1	-
Gastrointestinal		
Abdominal pain	2	-
Anorexia	1	1-10
Constipation	1	-
Dyspepsia/heartburn	-	1-10
Dysphagia	1	-
Flatulence	1	-
Jaundice	✔	-
Loose stools	1	-
Nausea	3	-
Pancreatitis	1	-
Genitourinary		
Micturition disorder	1	-
Nocturia	1	-
Sexual dysfunction	1	-

Adverse Events	Amlodipine	Hydrochlorothiazide
Urinary frequency	1	-
Hematological		
Agranulocytosis	-	<1
Anemia	-	<1
Leukopenia	-	<1
Purpura	1	-
Thrombocytopenia	1	<1
Laboratory Test Abnormalities		
Hepatic enzyme elevations	✔	-
Hypercalcemia	-	<1
Hyperglycemia	1	-
Hypokalemia	-	1-10
Musculoskeletal		
Arthrosis	1	-
Back pain	1	-
Malaise	1	-
Muscle cramps	1	-
Myalgia	1	-
Pain	1	-
Rhabdomyolysis	✔	-
Twitching	1	-
Renal		
Interstitial nephritis	-	<1
Renal failure	-	<1
Respiratory		
Eosinophilic pneumonitis	-	<1
Epistaxis	1	-
Respiratory distress	-	<1
Special Senses		
Conjunctivitis	1	-
Diplopia	1	-
Eye pain	1	-
Parosmia	1	-
Tinnitus	1	-
Xerophthalmia	1	-
Other		
Allergic reaction	1	<1
Angioedema	1	-
Fatigue	5	-
Gingival hyperplasia	1	-
Hepatic function impaired	-	<1
Hot flush	1	-
Pancreatitis	-	<1
Rigors	1	-
Weight gain	1	-
Weight loss	1	-

✔ Percent not specified
- Event not reported

Table 9. Boxed Warning for the Angiotensin II Receptor Antagonists[1]

WARNING
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, the combination angiotensin II receptor antagonist should be discontinued as soon as possible.

VII. Dosing and Administration

The usual dosing regimens for the angiotensin II receptor antagonists are listed in Table 10.

Table 10. Usual Dosing Regimens for the Angiotensin II Receptor Antagonists[1-18]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Candesartan	Heart Failure: Initial: 4 mg once daily; target: 32 mg once daily Hypertension: Initial: 16 mg once daily when used as monotherapy in patients who are not volume-depleted; maintenance: 8 to 32 mg per day in 1 or 2 divided doses	Children 1-17 years of age: Hypertension: 1 to 6 years of age: initial, 020 mg/kg per day; maintenance, 0.05 to 0.4 mg/kg per day 7-17 years of age (<50 kg): initial, 4 to 8 mg per day; maintenance, 2 to 16 mg per day 7-17 years of age (>50 kg): initial, 8 to 16 mg per day; maintenance, 4 to 32 mg per day	Tablet: 4 mg 8 mg 16 mg 32 mg
Candesartan and hydrochlorothiazide	Hypertension: Fixed-combination is not indicated for initial therapy; combination may be substituted for the titrated individual components; patients not controlled or experiencing hypokalemia on hydrochlorothiazide 25 mg can expect an incremental effect from Atacand HCT® 16 mg-12.5 mg; patients not controlled on Atacand® 32 mg can expect incremental blood pressure effects from Atacand HCT® 32 mg-12.5 mg and then 32 mg-25 mg	Safety and efficacy in children have not been established.	Tablet: 16 mg-12.5 mg 32 mg-12.5 mg 32 mg-25 mg
Eprosartan	Hypertension: Initial: 600 mg once daily when used as monotherapy in patients who are not volume-depleted; maintenance: 400 to 800 mg per day in 1 or 2 divided doses	Safety and efficacy in children have not been established.	Tablet: 400 mg 600 mg
Eprosartan and hydrochlorothiazide	Hypertension: Fixed-combination is not	Safety and efficacy in children have not been	Tablet: 600 mg-12.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; usual recommended dose is 600 mg-12.5 mg once daily when used in patients who are not volume-depleted; patients may be titrated to 600 mg-25 mg once daily	established.	600 mg-25 mg
Irbesartan	Diabetic Nephropathy: Target: 300 mg once daily Hypertension: Initial: 150 mg once daily in patients who are not volume-depleted; maximum: 300 mg once daily	Children 6-16 years of age: Hypertension: In a study at a dose of up to 4.5 mg/kg/day once daily, irbesartan did not appear to lower blood pressure effectively in pediatric patients aged 6 to 16 years.	Tablet: 75 mg 150 mg 300 mg
Irbesartan and hydrochlorothiazide	Hypertension: Initial: irbesartan 150 mg-HCTZ 12.5 mg once daily; maximum: 300 mg-25 mg once daily; in patients not controlled on monotherapy with irbesartan or HCTZ, the recommended doses of Avalide® in order of increasing mean effect are 150 mg-12.5 mg, 300 mg-12.5 mg and 300 mg-25 mg; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 150 mg-12.5 mg 300 mg-12.5 mg 300 mg-25 mg
Losartan	Diabetic Nephropathy: Initial: 50 mg once daily; dose should be increased to 100 mg once daily based on blood pressure response Hypertension: Initial: 50 mg once daily in patients who are not volume-depleted; maintenance: 25 to 100 mg per day in 1 or 2 divided doses Left Ventricular Hypertrophy in Hypertensive Patients: Initial: 50 mg once daily; hydrochlorothiazide 12.5 mg daily should be added and/or the losartan dose increased to	Children ≥6 years of age: Hypertension: Initial: 0.7 mg/kg once daily (up to 50 mg total); doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied	Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	100 mg once daily followed by an increase in hydrochlorothiazide 25 mg once daily based on blood pressure response		
Losartan and hydrochlorothiazide	Hypertension: Initial: losartan 50 mg-HCTZ 12.5 mg once daily; if blood pressure remains uncontrolled, the dose may be increased to 2 tablets of 50-12.5 mg once daily or 1 tablet of 100 mg-25 mg once daily; maximum 100 mg-25 mg per day Left Ventricular Hypertrophy in Hypertensive Patients: Initial: losartan 50 mg once daily; HCTZ 12.5 mg daily should be added or Hyzaar® 50 mg-12.5 mg substituted if blood pressure reduction is inadequate; if additional blood pressure reduction is needed, losartan 100 mg and HCTZ 12.5 mg or Hyzaar® 100 mg-12.5 mg may be substituted, followed by losartan 100 mg and HCTZ 25 mg or Hyzaar® 100 mg-25 mg	Safety and efficacy in children have not been established.	Tablet: 50 mg-12.5 mg 100 mg-12.5 mg 100 mg-25 mg
Olmesartan	Hypertension: Initial: 20 mg once daily when used as monotherapy in patients who are not volume depleted; maximum: 40 mg once daily	Children 6-16 years of age: Hypertension: 20 to <35 kg: initial, 10 mg once daily; maximum, 20 mg once daily ≥35 kg: initial, 20 mg once daily; maximum, 40 mg once daily	Tablet: 5 mg 20 mg 40 mg
Olmesartan and hydrochlorothiazide	Hypertension: Fixed-combination is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; in patients not controlled on olmesartan, HCTZ may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily; if patient is taking HCTZ, olmesartan may be added starting with a dose of 20 mg once daily and	Safety and efficacy in children have not been established.	Tablet: 20 mg-12.5 mg 40 mg-12.5 mg 40 mg-25 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	titrated to 40 mg		
Telmisartan	Cardiovascular Risk Reduction: 80 mg once daily Hypertension: Initial: 40 mg once daily; maximum: 80 mg per day	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg 80 mg
Telmisartan and amlodipine	Hypertension: Fixed combination may be substituted for its individually titrated components. Fixed combination may be used to provide additional blood pressure lowering for patients not adequately controlled on telmisartan alone or amlodipine alone. Initiate with 40/5 mg or 80/5 mg QD. Dosage may be increased after at least 2 weeks to a maximum dose of 80/10 mg QD.	Safety and efficacy in children have not been established.	Tablet: 40 mg-5 mg 40 mg-10 mg 80 mg-5 mg 80 mg-10 mg
Telmisartan and hydrochlorothiazide	Hypertension: Fixed-combination is not indicated for initial therapy; initiate combination therapy after failure on monotherapy; titrate dose by clinical effect; combination may be substituted for the titrated individual components; patients not controlled on telmisartan 80 mg monotherapy may be switched to Micardis HCT® 80 mg-12.5 mg once daily and titrated up to 160 mg-25 mg if necessary; patients not controlled on HCTZ 25 mg may be switched to Micardis HCT® 80 mg-12.5 mg or 80 mg-25 mg once daily; patients experiencing hypokalemia with HCTZ 25 mg may be switched to Micardis HCT® 80 mg-125 mg once daily	Safety and efficacy in children have not been established.	Tablet: 40 mg-12.5 mg 80 mg-12.5 mg 80 mg-25 mg
Valsartan	Heart Failure: Initial: 40 mg twice daily; up-titration to 80 to 160 mg twice daily should be done to the highest dose as tolerated; maximum: 320 mg in divided doses Hypertension: Initial: 80 to 160 mg once	Children 6-16 years of age: Hypertension: Initial: 1.3 mg/kg once daily (up to 40 mg total) administered as a tablet or suspension; doses above 2.7 mg/kg (or in excess of 160 mg) daily have not been studied	Tablet: 40 mg 80 mg 160 mg 320 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily when used as monotherapy in patients who are not volume depleted; maintenance: 80 to 320 mg once daily Post-Myocardial Infarction: Initial: 20 mg twice daily; target: 160 mg twice daily		
Valsartan and hydrochlorothiazide	Hypertension: Fixed-combination is not indicated for initial therapy; combination may be substituted for the titrated individual components; patients not controlled on valsartan monotherapy may switch to Diovan HCT® 80 mg-12.5 mg or 160 mg-12.5 mg once daily; if blood pressure remains uncontrolled, either valsartan or both components may be increased; patients not controlled or experiencing hypokalemia on HCTZ 25 mg may be switched to Diovan HCT® 80 mg-12.5 mg or 160 mg-12.5 mg once daily; maximum: valsartan 320 mg and HCTZ 25 mg	Safety and efficacy in children have not been established.	Tablet: 80 mg-12.5 mg 160 mg-12.5 mg 160 mg-25 mg 320 mg-12.5 mg 320 mg-25 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the angiotensin II receptor antagonists are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Angiotensin II Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypertension				
Lithell et al.[41] (2003) SCOPE Candesartan 16 mg/day vs placebo Patients also received conventional therapy with diuretics, ACE inhibitors, β-blockers, and calcium-channel blocking agents	DB, MC, PC, PG, RCT Patients 70-89 years of age with mild-to-moderate hypertension (SBP 160-179 mm Hg and/or DBP 90-99 mm Hg) and MMSE scores ≥24	N=4,964 3.7 years	Primary: First major coronary event including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke Secondary: cardiovascular death, nonfatal and fatal stroke and myocardial infarction, cognitive function	Primary: Results showed no significant difference in the primary end point between candesartan and placebo (P=0.19). Secondary: Candesartan treatment reduced nonfatal stroke by 27.8% (P=0.04) and all stroke by 23.6% (P=0.056) compared to placebo. There were no significant differences in myocardial infarction and cardiovascular mortality. Mean MMSE score fell from 28.5 to 28.0 in the candesartan group and from 28.5 to 27.9 in the control group (P=0.20). The proportion of patients who had a significant cognitive decline or developed dementia was not different in the 2 groups.
Baguet et al.[42] (2006) Candesartan 8 mg QD vs losartan 50 mg QD	DB, RCT Patients with mild-to-moderate essential hypertension (DBP 95-115 mm Hg)	N=256 6 weeks	Primary: Change in mean ambulatory DBP from baseline to the 0-24 hour period after the last dose of study medication Secondary:	Primary: At the end of the 6 weeks, the mean change in DBP between the baseline and the 0-24 hour period after the last dose of study medication was greater in patients receiving candesartan 8 mg compared with losartan (–7.3 vs –5.1 mm Hg; P<0.05) or placebo (0.3 mm Hg; P<0.001). Secondary: The mean change in SBP between the baseline and the 0-24 hour period after the last dose of study medication was greater in patients receiving candesartan (–10.8 mm Hg) or losartan (–8.8 mm Hg) than placebo (1.2 mm Hg;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			Change in mean ambulatory SBP from baseline to the 0-24 hour period after the last dose of study medication, change in DBP and SBP during the daytime and nighttime, change in DBP and SBP between 12 and 24 hours after dosing	P<0.001). Candesartan was associated with a greater reduction in DBP and SBP relative to placebo, when compared with losartan during both the daytime and nighttime, and between 12 and 24 hours after dosing (P<0.001). Both active treatments were well tolerated.
McInnes et al.[79] (2000) Candesartan 8 mg and HCTZ 12.5 mg QD vs lisinopril 10 mg and HCTZ 12.5 mg QD	DB, DD, MC, PG, RCT Patients 20-80 years of age with mild-to-moderate hypertension on prior antihypertensive monotherapy	N=355 26 weeks	Primary: Mean changes in DBP Secondary: Mean changes in SBP and heart rate, proportion of responders and controlled patients, safety	Primary: Changes in mean sitting DBP did not differ significantly between the groups (mean difference, 0.5 mm Hg; P=0.20). Secondary: No significant differences between the groups were reported for mean sitting SBP, heart rate, proportion of responders and controlled patients. Both drugs were well tolerated but a greater percentage of those in the lisinopril group (80% vs 69%) had a least one side effect (P=0.020). The proportion of patients spontaneously reporting cough (23.1% vs 4.6%) and discontinuing therapy due to adverse events (12.0% vs 5.9%) was also higher in the lisinopril group compared with the candesartan group.
Ohma et al.[80] (2000) Candesartan 16 mg and HCTZ 12.5 mg QD vs losartan 50 mg and	DB, MC, RCT Patients aged 20-80 years with mild-to-moderate uncontrolled hypertension while on monotherapy (any kind of medication)	N=340 12 weeks	Primary: Change in sitting DBP Secondary: SBP, proportion of responders, safety and tolerability	Primary: Greater reductions in DBP were reported with candesartan and HCTZ vs losartan and HCTZ (–10.4 vs –7.8 mm Hg; P=0.016). Secondary: Greater decreases in SBP were reported with candesartan and HCTZ (–19.4 mm Hg) vs losartan and HCTZ (–13.7 mm Hg; P=0.004). The proportion of patients achieving a DBP ≤90 mm Hg was greater with candesartan and HCTZ (60.9% vs 49.3%; P=0.044).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 12.5 mg QD				There were 8 withdrawals due to adverse effects in the candesartan and HCTZ group and 12 in the losartan and HCTZ group. The most common adverse effects were headache, tachycardia/palpitations, dizziness, and fatigue.
Fogari et al.[108] (2007) CANDIA Candesartan 16 mg and HCTZ 12.5 mg QD (single entity products) vs amlodipine 10 mg QD	DB, MC, RCT Patients, 20 to 80 years old, with mild to moderate uncomplicated hypertension not controlled on monotherapy with an antihypertensive (SBP <180 mg Hg and DBP 90 to 110 mg Hg)	N=203 8 weeks	Primary: Decrease in DBP Secondary: Sitting SBP, reduction of the orthostatic blood pressure at least two minutes after standing, change in heart rate, percentage of patients normalized (DBP <90 mm Hg and SBP <140 mm Hg), percentage of responders (reduction in DBP ≥5 mm Hg)	Primary: There was no significant difference in the mean decrease in DBP between treatment groups; the difference in final DBP was -0.02 mm Hg (95% CI, -1.48 to 1.52 mm Hg; P=0.979). Secondary: There was no significant difference between the groups at week 8 for the following: sitting SBP (P=0.835), heart rate (P<0.500), orthostatic SBP (P=0.883), orthostatic DBP (P=0.264), percentage of patients normalized (P=10), percentage of responders (P=0.900). The number of patients reporting an adverse event was greater in the amlodipine group (P=0.001). The number of patients reporting an adverse drug-related event was greater in the amlodipine group (P<0.001). Changes in blood chemistry and other secondary measurements were not significantly different between the treatment groups.
Robles et al.[43] (2008) ESTEPP Eprosartan 600 mg QD	MC, OL, PRO Patients with mild-to-moderate hypertension with and without diabetes, mean age 65 years for patients with diabetes and 63 years for patients without diabetes	N=549 16 weeks	Primary: Changes in blood pressure, compliance, adverse effects	Primary: Blood pressure decreased significantly (P<0.0001) in both diabetic and nondiabetic patients (SBP 25.9 vs 26.0 mm Hg), DBP (12.5 vs 13.2 mm Hg), MAP (16.9 vs 17.5 mm Hg) and pulse pressure (13.4 vs 12.8 mm Hg). Pulse pressure/MAP ratio showed a significant reduction in diabetics and nondiabetics. Treatment compliance did not differ between the groups (diabetics 98.0% vs nondiabetics 92.2%). The adverse effect rate was 7% in diabetic patients and 2.8% in nondiabetics.
Gradman et al.[113]	DB, MC, PC, PG,	N=652	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2005) Irbesartan 150 mg QD vs aliskiren 150 to 600 mg QD vs placebo	RCT Men and women, age 18 years or older, with mild-to-moderate essential hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	8 weeks	Change in mean sitting DBP and SBP Secondary: Proportion of patients achieving blood pressure control (<140/90 mm Hg), safety	Decreases in mean sitting DBP at 8 weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough DBP for aliskiren 150, 300 and 600 mg were 9.3, 11.8, and 11.5 mm Hg, respectively, versus 6.3 mm Hg for placebo. Decreases in mean sitting SBP at 8 weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough SBP for aliskiren 150, 300 and 600 mg were 11.4, 15.8, and 15.7 mm Hg, respectively, versus 5.3 mm Hg for placebo. The antihypertensive effect of aliskiren 150 mg was comparable to irbesartan 150 mg with reductions of 8.9 and 12.5 mm Hg for mean sitting DBP and SBP, respectively. Aliskiren 300 and 600 mg produced significantly greater mean sitting DBP reductions than irbesartan 150 mg (P<0.05). While the reductions in mean sitting SBP were greater with aliskiren 300 and 600 mg than irbesartan 150 mg, these differences were not statistically significant). Secondary: The percentage of patients achieving blood pressure control was significantly greater with all doses of aliskiren (37.8%-150 mg, 50.0%-300 mg, 45.7%-600 mg) and irbesartan (33.8%) compared to placebo (20.8%; P<0.05). More patients on aliskiren 300 and 600 mg achieved blood pressure control compared to irbesartan (P<0.05). Drug-related adverse events for both aliskiren and irbesartan were comparable to placebo and the most commonly reported adverse events were headache, dizziness, and diarrhea. The number of patients discontinuing therapy was similar in all groups.
Derosa et al.[112] (2005) Irbesartan 300 mg QD vs doxazosin 4 mg	DB, PG, RA Patients with type 2 diabetes and mild hypertension	N=96 1 year	Primary: Blood pressure, glucose metabolism and lipid parameters	Primary: Blood pressure was significantly reduced in both treatment groups compared with baseline (P<0.01). Irbesartan was significantly better in lowering blood pressure compared to doxazosin (P<0.05). Doxazosin significantly reduced glycosylated hemoglobin, fasting plasma glucose, fasting plasma insulin, total cholesterol, low density lipoprotein

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD				cholesterol, high density lipoprotein cholesterol, and triglycerides (P≤0.05 for all parameters). As monotherapy, neither of the drugs achieved adequate blood pressure control.
Neutel et al.[81] (2006) Irbesartan 150 to 300 mg and HCTZ 12.5 to 25 mg QD (fixed-dose combination) vs irbesartan 150 to 300 mg QD	AC, DB, MC, RCT Patients ≥18 years with severe hypertension who were untreated (seated DBP ≥110 mm Hg) or currently receiving antihypertensive monotherapy with DBP ≥100 mm Hg	N=737 7 weeks	Primary: Proportion of patients with DBP <90 mm Hg at week 5 Secondary: Proportion of patients who achieved seated SBP/DBP <140/90 mm Hg	Primary: Significantly more patients on combination therapy achieved seated DBP <90 mm Hg at week 5 compared with monotherapy (47.2% vs 33.2%; P=0.0005). Secondary: Significantly more patients attained SBP/DBP <140/90 mm Hg at week 5 (34.6% vs 19.2%, respectively; P<0.0001), while the mean difference between combination and monotherapy in seated DBP and SBP was 4.7 and 9.7 mm Hg, respectively (P<0.0001). Greater and more rapid blood pressure reduction with irbesartan plus HCTZ was achieved without additional side effects.
Neutel et al.[82] (2008) Irbesartan 300 mg and HCTZ 25 mg QD vs irbesartan 300 mg QD vs HCTZ 25 mg QD	AC, DB, RCT Patients with moderate hypertension (seated SBP 160-179 mm Hg when DBP <110 mm Hg; or DBP 100-109 mm Hg when SBP <180 mm Hg)	N=538 12 weeks	Primary: Change in SBP after week 8 Secondary: Change from baseline in DBP at weeks 8 and 12, SBP at week 12, proportion of responders (SBP <140 mm Hg and DBP <90 m Hg) at weeks 8 and 12	Primary: At week 8, there was a reduction in SBP of 27.1 mm Hg with irbesartan and HCTZ compared to 22.1 mm Hg with irbesartan monotherapy (P=0.0016) and 15.7 mm Hg with HCTZ (P<0.0001). Secondary: At week 8, there was a reduction in DBP of 14.6 mm Hg with irbesartan and HCTZ compared to 11.6 mm Hg with irbesartan monotherapy (P=0.0013) and 7.3 mm Hg with HCTZ (P<0.0001). A significantly greater percentage of patients reached a treatment goal of SBP <140 mm Hg and DBP <90 mm Hg by week 8 with irbesartan and HCTZ (53.4%) compared with irbesartan (40.6%; P=0.0254) and HCTZ (20.2%; P<0.0001) alone. Treatment was well tolerated in all 3 treatment groups with a slight increase in adverse events in the combination therapy group.
Weir et al.[83] (2007)	DB, MC, RCT (pooled analysis of	N=796	Primary: Antihypertensive	Primary: SBP/DBP reductions (27-31/16-22 mm Hg) were similar regardless of age,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Irbesartan 300 mg and HCTZ 25 mg QD (fixed-dose combination)	2 trials) Patients with stage 1 or 2 hypertension evaluated according to age	7-8 weeks	efficacy, tolerability	obesity and type 2 diabetes status and were greater in high- vs low-risk patients. Dizziness (2.0%-3.7%), hypotension (0%-0.7%), and syncope (0%) were rare and not centered in any subgroup. There was no hypotension in the elderly or in patients with type 2 diabetes.
Bobrie et al.[84] (2005) Irbesartan 150 mg and HCTZ 12.5 mg QD vs valsartan 80 mg and HCTZ 12.5 mg QD	OL, RCT Patients whose blood pressure remained uncontrolled after 5 weeks of HCTZ 12.5 mg QD	N=464 8 weeks	Primary: Blood pressure reductions, safety	Primary: Irbesartan and HCTZ produced greater reductions in average SBP and DBP measured by home blood pressure monitoring than valsartan and HCTZ (SBP, –13.0 vs –10.6 mm Hg; P=0.0094; DBP, –9.5 vs –7.4 mm Hg; P=0.0007). These differences were more pronounced in the morning than in the evening. Normalization rates observed with home blood pressure monitoring (SBP <135 mm Hg and DBP <85 mm Hg) were significantly greater with irbesartan and HCTZ than with valsartan and HCTZ (50.2% vs 33.2%; P=0.0003). The overall safety was similar in the 2 groups.
Stanton et al.[117] (2003) Losartan 100 mg QD vs aliskiren 37.5 to 300 mg QD	AC, DB, MC, RCT Men and women 21 to 70 years of age with mild-to-moderate hypertension (SBP ≥140 mm Hg)	N=226 4 weeks	Primary: Change in daytime ambulatory SBP Secondary: Changes in clinic SBP and DBP, plasma renin activity, plasma aliskiren levels, adverse events	Primary: A dose-dependent reduction in daytime ambulatory SBP was observed with increasing aliskiren doses (with mean changes of –0.40 mm Hg with aliskiren 37.5 mg, –5.3 mm Hg with aliskiren 75 mg, –8.0 mm Hg with aliskiren 150 mg, and –11 mm Hg with aliskiren 300 mg; P=0.0002). The change in daytime SBP with losartan 100 mg (–10.9 mm Hg) was significantly different than aliskiren 37.5 mg, but not the other higher aliskiren dosages). Secondary: Clinic SBP and DBP, both in the sitting and standing positions, decreased with aliskiren in a dose-dependent manner, whereas heart rate was unaltered. The decreases in clinic blood pressures were similar for losartan 100 mg and aliskiren 150 and 300 mg. Dose-dependent reductions in plasma renin activity were also observed (median change –55%, –60%, –77%, and –83% with 37.5, 75, 150 and 300 mg aliskiren, respectively; P=0.0008). By contrast, plasma renin activity increased by 110% with losartan 100 mg.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Rate of adverse events was 22% with aliskiren 37.5 mg, 35% with aliskiren 75 mg, 25% with aliskiren 150 mg, 23% with aliskiren 300 mg, and 32% with losartan 100 mg. There was no increase in the number of adverse events when increasing the dose of aliskiren.
Ribeiro et al.[114] (2007) LAMHYST Losartan 50 to 100 mg QD vs amlodipine 5 to 10 mg QD	DB, DD, RCT Males and females, age 18-79 years old, with diagnosis of mild (>95 mm Hg but <115 mm Hg) to moderate essential hypertension and not taking an antihypertensive medication (within last 4 weeks)	N=194 12 weeks	Primary: Difference between treatment groups in mean change in ABPM for last 9 hours of treatment and during drug holiday	Primary: After 12 weeks, mean reductions in SBP were significantly larger in the amlodipine group than the losartan group (–18.1 vs –10.1 mm Hg; P<0.001). Mean reductions in DBP were significantly larger in the amlodipine group than the losartan group (–18.1 vs –10.1 mm Hg; P<0.05). Mean increases in SBP were similar between the groups during the 2-day drug holiday (P>0.05). After the 2-day drug holiday, SBP was lower than baseline in both groups (P<0.001), with the amlodipine group SBP remaining significantly lower (P<0.01). Mean increases in DBP were similar between the groups during the 2-day drug holiday (P>0.05). After the 2-day drug holiday, DBP was lower than baseline in both groups (P=0.0001), with the amlodipine group DBP remaining significantly lower (P<0.05).
Oparil et al.[88] (1996) Losartan 50 to 100 mg QD vs amlodipine 5 to 10 mg QD If goal DBP (≤90 mm Hg) was not attained, drug doses could be doubled and/or	DB, DD, MC, RCT Patients with hypertension	N=900 12 weeks	Primary: Efficacy, tolerability, effects on quality of life	Primary: DBP reductions after 4, 8, and 12 weeks of therapy were clinically comparable (losartan group: 7.3, 10.4, and 11.1 mm Hg, respectively; amlodipine group: 7.9, 11.2, and 11.8 mm Hg, respectively; P=NS). Similar reductions in SBP were seen for both treatment groups (P value not significant). The percentage of patients reaching goal DBP (≤90 mm Hg) or DBP ≥90 mm Hg with a ≥10 mm Hg decrease from baseline) was comparable for the two groups, with 68% of patients in the losartan group and 71% of patients in the amlodipine group reaching goal. Significantly more patients in the amlodipine group had drug-related adverse experiences (27% vs 13%; P=0.029). Edema was more common in patients receiving the amlodipine regimen than in those receiving the losartan regimen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ mg was added.				(11% vs 1%; P=0.004). Overall quality of life was not different in the 2 treatment groups.
Dahlöf et al.[44] (2002) LIFE Losartan 50 to 100 mg QD vs atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential hypertension (sitting SBP/DBP 160-200 to 95-115 mm Hg) and LVH	N=9,193 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction and stroke Secondary: All-cause mortality, hospitalization for angina or heart failure, revascularization procedures, resuscitated cardiac arrest, new-onset diabetes	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference, P=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference, P=0.37). MAP was 102.2 and 102.4 mm Hg, respectively (P=NS). Heart rate decreased more in patients assigned to atenolol than losartan (–7.7 vs –1.8 beats/minute, respectively; P<0.0001). Compared to atenolol, the primary composite occurred in 13.0% fewer patients receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; P=0.021). While there was no difference in the incidence cardiovascular mortality (P=0.206) and myocardial infarction (P=0.491), losartan treatment resulted in a 24.9% relative risk reduction in stroke compared to atenolol (P=0.001). Secondary: A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (P=0.001). There was no significant difference among the other secondary end points between the 2 treatment groups. Note: At end point or end of follow-up, 18% and 26% of patients on losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16% and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Julius et al.[45] (2004) LIFE Black Subset Losartan 50 to 100 mg QD vs	Post hoc analysis Patients 55 to 80 years old with essential hypertension (sitting SBP/DBP 160-200/95-115 mm Hg) and LVH	N=523 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction and stroke	Primary: Compared with atenolol (11.2%), losartan in the United States African American population resulted in a greater incidence of the composite end point (17.4%; P=0.033). Hazard ratios favored atenolol across all parameters (P=0.246 for cardiovascular mortality, P=0.140 for myocardial infarction, and P=0.030 for stroke). In African American patients, blood pressure reduction was similar in both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.				groups, and regression of electrocardiographic-LVH was greater with losartan.
Lindholm et al.[46] (2002) LIFE Diabetic Subset Losartan 50 to 100 mg QD vs atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	Post hoc analysis Patients 55 to 80 years old with essential hypertension (sitting SBP/DBP 160-200/95-115 mm Hg) and LVH	N=1,195 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction and stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a 24% decrease in the primary composite end point (P=0.031). Losartan treatment resulted in a 37% risk reduction in cardiovascular deaths vs atenolol (P=0.028). Losartan treatment resulted in a 39% risk reduction in all-cause mortality vs atenolol (P=0.002). Mean blood pressure fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients. Secondary: Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively (RR, 0.61; P=0.002).
Kjeldsen et al.[47] (2002) LIFE Isolated Systolic Hypertension Subset Losartan 50 to 100 mg QD vs	Post hoc analysis Patients 55 to 80 years old with isolated systolic hypertension (SBP of 160-200 mm Hg and DBP <90 mm Hg) and LVH	N=1,326 ≥4 years	Primary: Composite of cardiovascular death, myocardial infarction, or stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a trend towards a 25% reduction in the primary end point (P=0.06). Losartan treatment resulted in a 46% risk reduction in cardiovascular mortality (P=0.01) and 40% risk reduction in stroke compared to atenolol (P=0.02). There was no difference in the incidence of myocardial infarction. Blood pressure was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atenolol 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.				Patients receiving losartan also had reductions in all-cause mortality (28%; P<0.046).
Flack et al.[116] (2003) Losartan 50 mg QD vs eplerenone 50 mg QD vs placebo Doses were increased if blood pressure remained uncontrolled.	DB, MC, PG, RCT Men and women ≥18 years old, with mild-to-moderate hypertension, with SBP <180 mm Hg and DBP 95 to 109 mm Hg (off medication) or if patients were receiving antihypertensive therapy their blood pressure was <140/90 mm Hg	N=551 16 weeks	Primary: Mean change from baseline in DBP at 16 weeks Secondary: Mean change from baseline at 16 weeks in SBP, SBP and DBP within and between racial groups, response rate (defined as the percentage of patients with DBP <90 mm Hg or DBP ≥90 mm Hg but ≥10 mm Hg below baseline), urinary albumin/creatinine ratio, effect of eplerenone in patients with various baseline renin and aldosterone levels, adverse effects	Primary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in DBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). Secondary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in SBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated African American patients (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the losartan-treated African American patients (P≤0.001). At 16 weeks, white patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated white patients (P=0.001). However, the difference in SBP- and DBP-lowering effects was not significant different between the eplerenone ad losartan groups (P=0.126, P=0.068, respectively). Significantly greater percentage of patients randomized to eplerenone exhibited a positive response to therapy compared to either placebo (64.5% vs 41.2%; P<0.001) or losartan group (64.5% vs 48.3%; P=0.003). The eplerenone group (regardless of race) exhibited statistically significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				improvement in urinary albumin/creatinine ratio from baseline compared to placebo (P=0.003). However, the difference in urinary albumin/creatinine ratio change from baseline was not significantly different between the eplerenone and losartan groups (P=0.652). Compared to losartan, eplerenone was more effective in lowering SBP and DBP in patients with low-moderate baseline renin levels (P<0.05). However, the difference was not statistically significant in patients with high baseline renin levels. Compared to losartan, eplerenone was more effective in lowering SBP in patients with low or high baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate baseline aldosterone levels. Compared to losartan, eplerenone was more effective in lowering DBP in patients with low baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate-high baseline aldosterone levels. There were no significant differences in the incidence of adverse events noted in eplerenone, placebo or losartan groups. The reported incidence of gynecomastia, breast pain, menstrual abnormalities, impotence, hyperkalemia and decreased libido with eplerenone was low and comparable to losartan and placebo.
Salerno et al.[85] (2004) Losartan 50 mg and HCTZ 12.5 mg QD vs losartan 50 to 100 mg QD	DB, RCT Patients with severe hypertension	N=585 6 weeks	Primary: Proportion of patients achieving goal blood pressure Secondary: Adverse events	Primary: Almost twice as many patients achieved goal blood pressure at 4 weeks on losartan 50 mg and HCTZ 12.5 mg vs losartan 50-100 mg monotherapy (P=0.002). Almost 3 times as many patients achieved goal blood pressure at 6 weeks with losartan and HCTZ vs losartan monotherapy (P<0.001). Adverse experiences on losartan and HCTZ (43%) were significantly less than with losartan monotherapy (53%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doses were titrated as needed to reach blood pressure goal (<90 mm Hg).				
Minami et al.[86] (2007) Losartan 50 mg and HCTZ 12.5 mg (single entity products) vs candesartan 8 mg QD or amlodipine 5 mg QD	OL Japanese outpatients with essential hypertension treated for at least 2 months with either candesartan or amlodipine and 24-hour ambulatory blood pressure ≥135/80 mm Hg	N=15 12 months	Primary: Changes in blood pressure	Primary: In patients who had previously received candesartan, 24-hour blood pressure decreased significantly from 137/89 mm Hg to 126/81 mm Hg after 3 months (P<0.05/P<0.001) and to 123/81 mm Hg after 12 months (P<0.01/P<0.001) of treatment with losartan and HCTZ. In patients who had previously received amlodipine, 24-hour blood pressure decreased significantly from 137/81 to 125/75 mm Hg after 3 months (P<0.05/P<0.05) and to 124/77 mm Hg after 12 months (P<0.05/P=NS) of treatment with losartan and HCTZ. There were significant decreases in SBP during the daytime, nighttime and early morning after 12 months in both groups. No adverse changes in the indices of glucose or lipid metabolism were observed in either group.
Lacourcière et al.[87] (2003) PROBE Losartan 50 mg and HCTZ 12.5 mg QD vs telmisartan 40 mg and HCTZ 12.5 mg QD vs	DB, MC, OL, RCT Patients ≥18 years of age with mild-to-moderate essential hypertension	N=597 6 weeks	Primary: Mean changes in ambulatory DBP Secondary: Mean changes in ambulatory SBP, 24-hour DBP, safety	Primary: During the last six hours of the dosing interval, telmisartan 40 mg plus HCTZ 12.5 mg and telmisartan 80 mg plus HCTZ 12.5 mg reduced mean DBP to a greater extent vs losartan 50 mg plus HCTZ 12.5 mg. Treatment differences between the groups were 1.8 mm Hg (P<0.05) and 2.5 mm Hg (P<0.001) lower, respectively, with the telmisartan and HCTZ arms. Secondary: Telmisartan 40 mg plus HCTZ 12.5 mg and telmisartan 80 mg plus HCTZ 12.5 mg produced greater reductions in ambulatory SBP vs losartan 50 mg plus HCTZ 12.5 mg of 2.5 and 3.4 mm Hg, respectively, during the last six hours of the dosing interval (P<0.05), and of 2.1 and 3.4 mm Hg, respectively, over the entire 24-hour dosing interval (P<0.05). Telmisartan 80 mg plus HCTZ 12.5 mg also lowered mean 24-hour DBP by 2.3 mm Hg more than losartan 50 mg plus HCTZ 12.5 mg (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
telmisartan 80 mg and HCTZ 12.5 mg QD				All treatments were well tolerated.
Brunner et al.[49] (2006) Olmesartan 20 mg QD vs candesartan 8 mg QD	DB, RCT Patients with mainly mild-to-moderate hypertension	N=635 8 weeks	Primary: 24-hour antihypertensive efficacy (with particular emphasis on blood pressure control during the early morning period), proportion of patients who achieved various ABPM goals (SBP/DBP <125/80 mm Hg)	Primary: After 8 weeks, significantly greater proportions of patients treated with olmesartan achieved 24-hour and daytime ABPM goals 25.6% and 18.3%, respectively) compared with candesartan (14.9%; P<0.001 and 9.6%; P=0.002, respectively). During the last 4 hours of 24-hour ABPM, the proportion of patients who achieved goals was significantly greater with olmesartan (33.3%) than candesartan (22.9%; P<0.001). Similarly, during the last 2 hours of 24-hour ABPM, the proportion of patients who achieved these blood pressure goals was higher with olmesartan (26.9% and 19.9%) compared to candesartan (19.6%; P=0.028 and 14.3%; P=0.061).
Oparil et al.[48] (2001) Olmesartan 20 mg QD vs irbesartan 150 mg QD, losartan 50 mg QD or valsartan 80 mg QD	DB, MC, PG, RCT Patients ≥18 years old (mean age 52 years) with essential hypertension (cuff DBP ≥100 mm Hg and ≤115 mm Hg and mean daytime DBP ≥90 mm Hg and <120 mm Hg)	N=588 8 weeks	Primary: Change in seated cuff DBP at week 8 Secondary: Change in seated cuff SBP at week 8, 24-hour DBP and SBP, adverse events	Primary: The mean reductions in seated cuff DBP at week 8 were significantly greater with olmesartan (11.5 mm Hg) than with irbesartan (9.9 mm Hg; P=0.0412), losartan (8.2 mm Hg; P=0.0002) and valsartan (7.9 mm Hg; P<0.0001). The clinical significance of a few mm Hg DBP difference between the groups is unknown. Secondary: Reductions of cuff SBP were not significantly different among the 4 ARBs and ranged from 8.4 to 11.3 mm Hg. The reduction in mean 24-hour DBP with olmesartan (8.5 mm Hg) was significantly greater than reductions with losartan and valsartan (6.2 and 5.6 mm Hg, respectively) and showed a trend toward significance when compared to irbesartan (7.4 mm Hg; P=0.087). The reduction in mean 24-hour SBP with olmesartan (12.5 mm Hg) was significantly greater than the reductions with losartan and valsartan (9.0 and 8.1 mm Hg, respectively) and equivalent to the reduction with irbesartan

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				(11.3 mm Hg). All drugs were well tolerated with the incidence of adverse events reported in 30.6% of patients in the olmesartan group, 35.6% for irbesartan, 32.0% for losartan, and 44.8% for valsartan.
Chrysant et al.[89] (2004) Olmesartan 10 to 40 mg QD and HCTZ 12.5 to 25 mg QD vs olmesartan 10 to 40 mg QD vs HCTZ 12.5 to 25 mg QD vs placebo	DB, RCT, factorial design Patients with a baseline mean seated DBP of 110-115 mm Hg	N=502 8 weeks	Primary: Change in DBP at week 8 Secondary: Change in SBP at week 8	Primary: Olmesartan and HCTZ produced greater reductions in seated DBP at week 8 than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared with placebo in a dose-dependent manner. Reductions in mean trough DBP were 8.2, 16.4 mm Hg, and 21.9 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively. Secondary: Olmesartan and HCTZ produced greater reductions in seated SBP at week 8 than did monotherapy with either component. All olmesartan and HCTZ combinations significantly reduced DBP compared with placebo in a dose-dependent manner. Reductions in mean trough SBP were 3.3, 20.1, and 26.8 mm Hg with placebo, olmesartan 20 mg plus HCTZ 12.5 mg, and olmesartan 40 mg plus HCTZ 25 mg, respectively. All treatments were well tolerated.
Kereiakes et al.[90] (2007) Olmesartan 20 mg/day for 2 weeks, then 40 mg/day for 2 weeks then olmesartan/HCTZ 40/12.5 mg/day (fixed-dose	DB, DD, MC, PG, RCT Patients with stage 2 hypertension (mean seated DBP ≥90 mm Hg but <115 mm Hg and SBP ≥160 mm Hg but <200 mm Hg or DBP ≥100 mm Hg	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining blood pressure goals of	Primary: Patients treated with olmesartan/HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril/amlodipine (least square mean change, –32.5 vs –26.5 mm Hg; P=0.024; least square mean treatment difference, –6.0 mm Hg; 95% CI, –11.1 to –0.8 mm Hg). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan/HCTZ compared with benazepril/amlodipine at week 12 (P=0.056).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination) for 4 weeks increased to 40/25 mg for 4 weeks vs benazepril 10 mg/day for 2 weeks, then 20 mg/day for 2 weeks, then benazepril 20 mg/day plus amlodipine 5 mg/day for 4 weeks, then benazepril 20 mg/day plus amlodipine 10 mg/day for 4 weeks	but <115 mm Hg)		<140/90 mm Hg, <130/85 mm Hg, and <130/80 mm Hg	The percentage of patients achieving goal rates at the end of the study for olmesartan/HCTZ and benazepril/amlodipine were 66.3% and 44.7% (P=0.006) for <140/90 mm Hg, 44.9% vs 21.2% (P=0.001) for <130/85 mm Hg, and 32.6% and 14.1% (P=0.006) for <130/80 mm Hg. Both treatments were well tolerated.
Chrysant et al.[98] (2008) COACH Olmesartan 10 to 40 mg QD vs amlodipine 5 to 10 mg QD vs	DB, MC, PC, RCT Patients, age 18 years and older, with seated DBP of 95 to 120 mm Hg	N=1,940 8 weeks	Primary: Change from baseline in seated DBP at week 8 Secondary: Change from baseline in seated SBP at week 8, mean change from baseline in seated DBP and SBP at weeks 2, 4, 6 and 8 without last observation carried	Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week 8 (P<0.001). Reductions in seated DBP with monotherapy treatment ranged from –8.3 to –12.7 mm Hg; reductions with combination therapy ranged from –13.8 to –19.0 mm Hg. All combinations reduced seated DBP significantly greater than either component as monotherapy at the same dosage (P<0.001). Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week 8 (P<0.001 for treatment, P=0.024 for placebo). All combinations reduced seated SBP significantly greater either component as monotherapy at the same dosage (P<0.001). The proportion of patients achieving goal BP were:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
olmesartan 10 to 40 mg and amlodipine 5 to 10 mg QD vs placebo			forward, proportion of patients achieving BP goal (<140/90 mm Hg or <130/80 mm Hg), safety	20.0% to 36.3% of patients receiving olmesartan monotherapy 21.1% to 32.5% of patients receiving amlodipine monotherapy 35.0% to 53.2% of patients receiving combination therapy 8.8% of patients receiving placebo. Combination therapy resulted in significantly greater achievement of goal BP than monotherapy (P<0.005). No difference in overall rates of adverse events across the different treatment groups was seen. Nearly 27% of patients experienced a drug-related adverse event. Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment: none of the changes were considered clinically significant. Platelet counts increased significantly from baseline (statistically) for patients receiving amlodipine, however the increase was <10% and not deemed clinically relevant.
Xi et al.[50] (2008) Telmisartan vs losartan	MA Patients with hypertension	N=1,832 (11 trials) Variable duration	Primary: Reduction in DBP and SBP Secondary: Therapeutic response of DBP and SBP, tolerability	Primary: Use of telmisartan resulted in a significant reduction in clinic DBP (WMD, 1.52; 95% CI, 0.85 to 2.19) and SBP (WMD, 2.77; 95% CI, 1.90 to 3.63) when compared with losartan. Secondary: There was also a significant reduction in 24-hour mean ambulatory DBP (WMD, 2.49; 95% CI, 0.56 to 4.42) and SBP (WMD, 2.47; 95% CI, 0.40 to 4.55) with telmisartan as compared to losartan. There was a significant increase in therapeutic response of DBP (RR, 1.14; 95% CI, 14 to 1.23) and SBP response (RR, 1.10; 95% CI, 11 to 1.20) with telmisartan as compared to losartan. Both telmisartan and losartan were well tolerated.
Karlberg et al.[91] (1999) TEES	DB, DD, MC, PG, RCT Elderly patients (≥65 years) with	N=278 26 weeks	Primary: Change from baseline in supine SBP and DBP	Primary: Both treatments showed comparable decreases in blood pressure. Mean changes in DBP were –12.8 mm Hg for telmisartan and –11.4 mm Hg for enalapril (P=0.074). Mean changes in SBP were –22.1 mm Hg for telmisartan and –20.1 mm Hg for enalapril (P=0.350).

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Telmisartan 20 to 80 mg QD vs enalapril 5 to 20 mg/day HCTZ 12.5 or 25 mg QD was added as needed to reach DBP goal (≤90 mm Hg)	mild-to-moderate hypertension received telmisartan or enalapril and HCTZ was added at week 12 if needed		Secondary: Proportion of responders, safety	Secondary: Overall, 63% and 62% of patients responded to telmisartan and enalapril, respectively, with a DBP of <90 mm Hg. Both regimens provided effective blood pressure lowering over the 24-hour dosing interval, as determined by ambulatory blood pressure monitoring. Both regimens were well tolerated; however, the enalapril group had a higher incidence of cough than the telmisartan group (15.8% vs 6.5%).
Sharma et al.[123] (2007) Telmisartan-amlodipine (T+A) 40/5 mg QD (fixed-dose combination) vs amlodipine (A) 5 mg QD	RCT, DB, MC Patients 18 to 65 years of age with established stage II uncomplicated essential hypertension	N=210 12 weeks	Primary: SBP/DBP reductions and responder rates (SBP/DBP <130/<80 mm Hg)	Primary: There was a significant reduction from baseline in mean SBP in both groups (T+A, from 176.3 to 128.0 mm Hg; A, from 171.8 to 143.4 mm Hg; both, P<0.05 vs baseline). There was a significant reduction in SBP from baseline in the T+A and A groups (–27.4% and –16.6%, respectively; P<0.05 within group and between groups). There was a significant reduction from baseline in mean DBP in both treatment groups (T+A, from 100.9 to 93.8 mm Hg; A, from 99.7 to 94.3 mm Hg; both, P<0.05). There was a 20.2% reduction in mean DBP in the T+A group, which was significantly greater compared with the reduction of 12.7% observed in the A group (P<0.05 between groups and within both groups). A total of 87.3% of patients receiving T+A reached the target SBP/DBP goal, compared to 69.3% of patients receiving A (P<0.05). A total of 16.0% of patients in the T+A group experienced AEs compared with 15.4% of patients in the A group (P=NS). The most common AEs in the T+A group were peripheral edema (8.5%), headache (5.7%), dizziness and cough (3.8%), and diarrhea (1.9%).
Littlejohn et al.[122] (2009) Telmisartan 20 to	RCT, DB, PC, MC Patients ≥18 years of age with Stage 1	N=2,607 8 weeks	Primary: Change in the in-clinic seated diastolic BP	Primary: Both telmisartan (irrespective of amlodipine dosage; P<0.0001) and amlodipine (irrespective of telmisartan dosage; P<0.0001) significantly lowered the in-clinic DBP.

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80 mg and amlodipine 2.5 to 10 mg QD vs telmisartan 20 to 80 mg QD vs amlodipine 2.5 to 10 mg QD vs placebo	or 2 hypertension (diastolic BP ≥95 and ≤119 mm Hg)		Secondary: Change in the in-clinic seated systolic BP, DBP and SBP response (DBP <90 mm Hg, decrease in DBP ≥10 mm Hg, SBP <140 mm Hg, decrease in SBP ≥15 mm Hg), and BP control (DBP <90 mm Hg and SBP <140 mm Hg)	The greatest reduction in BP was with telmisartan 80 mg plus amlodipine 10 mg (SBP/DBP -26.4/-20.1 mm Hg; P<0.05 vs both monotherapies). DBP and SBP response was achieved by 91.2% and 90.4% of patients in the telmisartan 80 mg plus amlodipine 10 mg group, respectively. More than 50% of patients treated with combination therapy achieved BP control, with the highest percentages (76.5% [overall control] and 85.3% [diastolic BP control]) being achieved by patients treated with telmisartan 80 mg plus amlodipine 10 mg. A total of 37.3% of patients reported at least 1 adverse event. The most commonly reported adverse events were headache (5.4%) and peripheral edema (4.4%). Headache was more frequent in the placebo group (10.9%) compared with the telmisartan monotherapy (5.9%), amlodipine monotherapy (6.0%), and combination therapy (4.7%). The incidence of peripheral edema was highest in the amlodipine 10-mg group (17.8%); however, this rate was lower when amlodipine was used in combination with telmisartan: 11.4% (telmisartan 20 mg/amlodipine 10 mg), 6.2% (telmisartan 40 mg/amlodipine 10 mg), and 11.3% (telmisartan 80 mg/amlodipine 10 mg).
Maciejewski et al.[119] (2006) Valsartan 80 to 160 mg QD vs amlodipine 5 to 10 mg QD If blood pressure exceeded 140/90 while on highest treatment dose,	DB, PRO, RCT, XO African-Americans, older than 35 years, with baseline blood pressure >140/90 mm Hg and not on antihypertensive treatment	N=20 8-10 weeks for each arm with 2 week washout period before crossover	Primary: Comparison of 24 hour ABPM recordings Secondary: Magnitude of change from baseline in SBP and DBP with each treatment, percent of patients who achieved goal <140/<90 with each treatment based on clinic	Primary: There was no difference between the groups based on 24 hour ABPM: SBP amlodipine 130±8 vs valsartan 127±17 (P=0.350) and DBP amlodipine 82±5 vs valsartan 84±16 (P=0.430). Secondary: There was no difference between groups in magnitude of change from baseline in blood pressure (amlodipine -25±8/-18±7 vs valsartan -25±9/-16±7; P=0.61), and in percent of patients achieving goal blood pressure, 70% in the valsartan group and 75% in the amlodipine group (P=0.62).

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HCTZ 12.5mg/day was added to the regimen.			blood pressure measurements	
Ichihara et al.[120] (2006) Valsartan 40 to 160 mg QD vs amlodipine 2.5 to 10 mg QD	RCT Patients with untreated hypertension (clinic SBP >140 mm Hg and/or DBP >90 mm Hg; or ABPM SBP >135 mm Hg and/or DBP >98 mm Hg)	N=100 12 months	Primary: ABPM and clinic blood pressure Secondary: Pulse wave velocity, carotid intima-media thickness, urinary albumin excretion	Primary: Both treatments resulted in significant decreases in blood pressure, both ambulatory and clinic, over 12 months from baseline; blood pressure decreases were similar between treatment groups (Between treatments: clinic SBP P=0.34; clinic DBP P=0.85; 24 hour ABPM P=0.14). Blood pressure variability decreased significantly in the amlodipine group compared to the valsartan group, where there was no change in blood pressure variability (P<0.01). Secondary: The decrease in pulse wave velocity was significant from baseline for both groups, but not significantly different from each other (P<0.05 from baseline). Intima-media thickness was not changed significantly from baseline for either treatment (P>0.05 for both from baseline). Urinary albumin excretion in the valsartan group decreased significantly both from baseline and compared to amlodipine treatment (P<0.05 from baseline, P value for comparison not reported).
White et al.[126] (2008) Val-DICTATE Valsartan-HCTZ 160/12.5 mg QD (fixed-dose combination) vs HCTZ 25 mg QD	RCT, DB, MB Patients with stage 1-2 hypertension whose BP remained uncontrolled on HCTZ 12.5 mg	4 weeks	Primary: Percentage of patients whose clinic BP values were <140/90 mm Hg and blood pressure values	Primary: A significantly higher proportion of hypertensive patients met blood pressure control levels in the valsartan/HCTZ group (37%) compared with the HCTZ group (16%; P<0.001). Changes in SBP and DBP were significantly greater with valsartan/HCTZ (-12. 4/-7.5 mm Hg) compared to HCTZ (-5.6/-2.1 mm Hg; P<0.001).
Waeber et al.[92]	OL, RCT	N=327	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Valsartan 80 mg QD, which was switched to valsartan 80 mg and HCTZ 12.5 mg QD or valsartan 80 mg and benazepril 10 mg QD	Patients with mild-to-moderate uncontrolled hypertension (DBP ≥90) while on valsartan monotherapy	4 weeks	Efficacy and safety	The 2 combinations produced an additional blood pressure reduction compared to monotherapy (both P<0.001), with similar DBP reductions reported for the 2 combination groups (–4.5 mm Hg with valsartan plus HCTZ and –3.3 mm Hg with valsartan plus benazepril). SBP reductions of – 6.7 and –3.2 mm Hg with valsartan plus HCTZ and valsartan plus benazepril, respectively, were reported (P=0.1). At the end of the trial, the blood pressure of the responders to valsartan monotherapy was lower than that of patients requiring combination therapy. Valsartan given alone or in association with HCTZ or benazepril was well tolerated.
Schweizer et al.[93] (2007) Valsartan 160 mg and HCTZ 25 mg QD (fixed-dose combination)	OL Hypertensive patients not adequately controlled by free combination of candesartan and HCTZ for 4 weeks	N=197 8 weeks	Primary: Reduction in mean sitting DBP between week 4 and 8 Secondary: Reduction in mean sitting SBP from week 4 to 8	Primary: At baseline, DBP was 103.0 mm Hg. After 4 weeks of candesartan and HCTZ, DBP decreased to 93.8 mm Hg. Subsequent treatment with valsartan and HCTZ for 4 additional weeks reduced DBP to 88.7 mm Hg. This represented an additional decrease in DBP of 5.1 mm Hg (P<0.0001). Secondary: The valsartan and HCTZ fixed-dose combination reduced SBP by 3.4 mm Hg (P=0.0029).
Fogari et al.[94] (2006) Valsartan 160 mg and HCTZ 12.5 mg QD vs olmesartan 20 mg and HCTZ 12.5 mg QD	PRO, PG, RCT Hypertensive patients aged 35-75 years with DBP 90-110 mm Hg after 4 weeks of monotherapy on either valsartan or olmesartan	N=130 8 weeks (4 weeks of combination therapy)	Primary: Changes in blood pressure	Primary: Both combinations induced a greater ambulatory blood pressure reduction than monotherapy. However, mean reduction from baseline in the valsartan and HCTZ-treated patients (–21.5/–14.6 mm Hg for 24 hours, –21.8/–14.9 mm Hg for daytime, and –20.4/–13.7 mm Hg for nighttime SBP/DBP) was greater than in the olmesartan and HCTZ-treated patients (–18.8/–12.3 mm Hg for 24 hours, –19.3/–12.8 mm Hg for daytime, and –17.4/–10.6 mm Hg for nighttime SBP/DBP). The difference between the effects of the 2 treatments was significant (P<0.01). Plasma concentrations of HCTZ were significantly greater with valsartan than with olmesartan at each determination time (P<0.05).
White et al.[95] (2008)	DB, PC, RCT	N=1,181	Primary: Changes in DBP	Primary: Changes from baseline in blood pressure following telmisartan and HCTZ

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Valsartan 160 mg and HCTZ 25 mg QD vs telmisartan 80 mg and HCTZ 25 mg QD vs placebo	Hypertensive patients	8 weeks	and SBP at 8 weeks Secondary: Safety	(–24.6/–18.2 mm Hg) were significantly greater than both valsartan and HCTZ (–22.5/–17.0 mm Hg; P=0.017 for SBP and P=0.025 for DBP), and placebo (–4.1/–6.1 mm Hg; P<0.0001). Secondary: The total number of patients with at least 1 adverse event reported was similar among the 3 treatment groups and was 37% for valsartan and HCTZ, 36% for telmisartan and HCTZ, and 42% for placebo.
Sharma et al.[96] (2007) SMOOTH Valsartan 160 mg for 4 weeks with add-on HCTZ 12.5 mg for 6 weeks vs telmisartan 80 mg for 4 weeks and add-on HCTZ 12.5 mg for 6 weeks	MC, PRO, OL, RCT, blinded-end point Men and women aged ≥30 years with mild-to-moderate hypertension (mean seated SBP 140-179 mm Hg and/or DBP 95-109 mm Hg), with type 2 diabetes and BMI >27 kg/m^2	N=840 10 weeks	Primary: Change in mean ambulatory SBP and DBP	Primary: At 10 weeks, telmisartan and HCTZ provided significantly greater reductions in the last 6 hours of mean ambulatory blood pressure (differences in SBP were 3.9 mm Hg; P<0.0001 and differences in DBP were 2.0 mm Hg; P=0.0007). Telmisartan and HCTZ also produced significantly greater reductions than valsartan and HCTZ in 24-hour mean ambulatory blood pressure (differences in SBP were 3.0 mm Hg; P=0.0002 and differences in DBP were 1.6 mm Hg; P=0.0006) and during morning, daytime and nighttime periods (P<0.003). Both treatments were well tolerated.
Calhoun et al.[105] (2009) Valsartan-HCTZ 320/25 mg QD vs	DB, MC, RCT Patients 18 to 85 years of age with moderate to severe essential hypertension	N=2,271 8 weeks	Primary: Difference in mean sitting diastolic blood pressure and mean sitting systolic blood pressure	Primary: At each assessment after week 3, a significantly greater proportion of patients receiving triple therapy achieved overall BP control (<140/90 mm Hg) compared with those receiving any of the dual therapies (all P<0.0001). At end point, 70.8% of patients in the triple-therapy group achieved control, compared with 48.3% for valsartan/HCTZ, 54.1% for amlodipine/valsartan,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine-valsartan 10/320 mg QD vs amlodipine-HCTZ 10/25 mg QD vs amlodipine-valsartan-HCTZ 10/320/25 mg QD				and 44.8% for amlodipine/HCTZ (all P<0.0001). Triple therapy with amlodipine/valsartan/HCTZ improved BP control significantly better than any of the dual therapies.
Conlin et al.[52] (2000) PREVAIL Candesartan 8 to 16 mg QD, irbesartan 150 to 300 mg QD, losartan 50 to 100 mg QD, and valsartan 80 to 160 mg QD vs another ARB vs ARB plus low-dose HCTZ	MA Patients with hypertension	N=11,281 (43 trials) Duration varied	Primary: Weighted average for SBP and DBP reduction with ARB monotherapy, dose titration, and with the addition of low-dose HCTZ were calculated; responder rates	Primary: The absolute weighted-average reductions in DBP (8.2 to 8.9 mm Hg) and SBP (10.4 to 11.8 mm Hg) for ARB monotherapy were comparable for all ARBs. Responder rates for ARB monotherapy were 48% to 55%. Dose titration resulted in slightly greater blood pressure reductions and an increase in responder rates of 53% to 63%. ARB and HCTZ combinations produced substantially greater reductions in SBP (16.1 to 20.6 mm Hg) and DBP (9.9 to 13.6 mm Hg) than ARB monotherapy. Responder rates for ARB and HCTZ combinations were 56% to 70%. The authors concluded that candesartan, irbesartan, losartan and valsartan produced comparable antihypertensive efficacy when administered at their recommended doses, a near flat dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Heart Failure				
Cohn et al.[54] (2001) Val-HeFT Valsartan 160 mg BID vs placebo	DB, PC, RCT Patients ≥18 years old with a cardiovascular history and NYHA II-IV heart failure	N=5,010 2 years	Primary: Mortality and composite end point of morbidity and mortality Secondary: Change in NYHA class, ejection fraction, signs and symptoms of heart failure, quality of life	Primary: Compared with placebo, valsartan resulted in no significant differences in all-cause mortality. Patients treated with valsartan experienced a 13% decrease in the composite end point (P=0.009) and 27% decrease in heart failure hospitalizations (P<0.001). Secondary: Treatment with valsartan resulted in significant improvements in NYHA class, ejection fraction, signs and symptoms of heart failure and quality of life as compared with placebo (P<0.01). In a post hoc analysis of the combined end point and mortality in subgroups defined according to baseline treatments with ACE inhibitors or β-blockers, valsartan had a favorable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs.
Pfeffer et al.[55] (2003) CHARM Overall Programme Candesartan 32 mg daily (±ACE inhibitor) vs placebo (±ACE inhibitor)	DB, PC, PG, RCT Summary of all CHARM sub-studies	N=7,599 37.7 months	Primary: All-cause mortality (Overall Programme) and cardiovascular death or hospital admission for CHF (all of the component trials)	Primary: In the overall analysis, candesartan 32 mg daily resulted in an 18% decreased risk of all-cause mortality compared to placebo (23% vs 25%; unadjusted HR, 0.91; 95% CI, 0.83 to 10; P=0.055; covariate adjusted HR, 0.90; 95% CI, 0.82 to 0.99; P=0.032). Annual mortality rates were 8.1% and 8.8% for patients treated with candesartan and placebo, respectively. The lower mortality in patients treated with candesartan vs placebo was attributed to fewer cardiovascular deaths (18% vs 20%; unadjusted HR, 0.88; 95% CI, 0.79 to 0.97; P=0.012). Hospital admissions for CHF were significantly fewer in patients treated with candesartan than placebo (20% vs 24%; P<0.0001).
McMurray et al.[56] (2003) CHARM-Added	DB, MC, PC, RCT Patients ≥18 years old with LVEF	N=2,548 41 months	Primary: Composite of cardiovascular death and	Primary: Compared to placebo, candesartan 32 mg daily when added to ACE inhibitors resulted in a 15% reduction in the primary end point (P=0.011), 16% decrease in cardiovascular deaths (P=0.029) and 17% reduction in heart failure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Candesartan 32 mg daily in patients already taking ACE inhibitors vs placebo in patients already taking ACE inhibitors	≤40%, NYHA II-IV heart failure and treatment with an ACE inhibitor at a constant dose for 30 days or longer		hospitalization for heart failure Secondary: Composites of primary end point and myocardial infarction, nonfatal stroke and coronary revascularization	hospitalizations (P=0.014). Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, myocardial infarction, stroke, or coronary revascularization in the candesartan group (42.9%) compared to placebo (46.9%; P=0.015).
Granger et al.[57] (2003) CHARM-Alternative Candesartan 32 mg daily vs placebo	DB, PC, RCT Patients ≥18 years old with LVEF ≤40%, NYHA II-IV heart failure and intolerance to ACE inhibitors	N=2,028 33.7 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and myocardial infarction, nonfatal stroke and coronary revascularization	Primary: Compared to placebo, candesartan 32 mg daily resulted in a 30% reduction of the composite end point (P<0.0001). A 20% decrease in cardiovascular death (P=0.02) and 39% reduction in heart failure hospitalizations (P<0.0001) were noted in patients treated with candesartan compared to placebo. Study drug discontinuation rates were similar in the candesartan (30%) and placebo (29%) groups. Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, myocardial infarction, stroke, or coronary revascularization in the candesartan group (39.1%) compared to placebo (44.9%; P<0.0001).
Yusuf et al.[58] (2003) CHARM-Preserved Candesartan 32 mg daily vs	DB, PC, RCT Patients ≥18 years old with preserved ejection fraction (>40%) and symptomatic heart failure	N=3,025 36.6 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and myocardial	Primary: Compared to placebo, candesartan 32 mg daily resulted in an insignificant 14% trend towards lower incidence of the primary end point (P=0.051). Candesartan significantly reduced the risk of heart failure hospitalization (16%; P=0.047) but did not significantly decrease the risk of cardiovascular death (P=0.635). Secondary: The composite of cardiovascular death, hospitalization for CHF, myocardial infarction and stroke was significantly lower in the candesartan group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			infarction, nonfatal stroke and coronary revascularization	compared to placebo (25.6% vs 28.4%; P=0.037). There was no significant difference in the composite of cardiovascular death, hospital admission for CHF, myocardial infarction, stroke, or coronary revascularization in the candesartan group (30.4%) compared to placebo (32.9%; P=0.130).
Chan et al.[110] (2007) Candesartan 8 mg in addition to spironolactone 25 mg QD (combination group) vs candesartan 8 mg in addition to placebo (control group)	DB, PC, RCT Patients with LVEF <40% on ACE inhibitors for >6 months	N=48 1 year	Primary: Change in LVEF, left ventricular end-diastolic volume index, end-systolic volume index, left ventricular mass index, SBP, quality of life	Primary: At 1 year, combination therapy was associated with a significant improvement in LVEF from baseline (P<0.01). At 1 year, combination therapy was associated with a significant reduction in left ventricular end-diastolic volume index from baseline (P<0.001). At 1 year, combination therapy was associated with a significant reduction in end-systolic volume index from baseline (P<0.0005). At 1 year, combination therapy was associated with a significant reduction in left ventricular mass index from baseline (P=0.002). At 1 year, combination therapy was associated with a significant reduction in SBP from baseline (P<0.05). The control group was not associated with significant improvements in any of the above primary outcome measures. The quality of life score improved in both study groups.
Pitt et al.[59] (1997) ELITE Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥65 years with symptomatic heart failure (NYHA class II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=722 1 year	Primary: Change in renal function Secondary: Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups). Secondary: Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, –4% to +55%; P=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8% vs 8.7%; risk reduction, 46%; 95% CI, 5% to 69%; P=0.035).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			failure, NYHA class, admission for myocardial infarction or unstable angina	Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to the hospital for any reason was less frequent with losartan than with captopril treatment (22.2% vs 29.7%; P=0.014). More patients discontinued therapy due to adverse events with captopril (20.8%) than losartan (12.2%; P=0.002).
Pitt et al.[60] (2000) ELITE II Captopril 50 mg TID vs losartan 50 mg QD	DB, MC, PG, RCT Patients ≥60 years old with symptomatic heart failure (NYHA II–IV and LVEF ≤40%), and no history of prior ACE inhibitor therapy	N=3,152 555 days (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35; P=0.16). Secondary: Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI, 0.98 to 1.60; P=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7% vs 14.7%; P<0.001), including cough (0.3% vs 2.7%). Note: The ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial which reported a greater reduction in all-cause mortality with losartan compared with captopril.
McKelvie et al.[61] (1999) RESOLVD Enalapril 10 mg BID vs candesartan 4 to 16 mg QD vs	DB, PG, MC, RCT Patients with CHF (NYHA classes II to IV), a 6 minute walk distance of 500 meters or less, and an ejection fraction <40%	N=768 43 weeks	Primary: Change in 6-minute walk distance Secondary: Change in NYHA functional class, quality of life, ejection fraction, ventricular volumes, neurohormone levels, safety	Primary: There were no significant differences among the groups with regards to the 6-minute walk distance over the 43-week study period. Secondary: There were no significant differences among the groups with regards to the NYHA functional class or quality of life at 18 or 43 weeks. Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (P=NS). End-diastolic volumes (P<0.01) and end-systolic volumes (P<0.05) increased less with combination therapy than with monotherapy with either agent.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination candesartan 4 to 8 mg QD and enalapril 10 mg BID				Aldosterone decreased with combination therapy at 17 but not 43 weeks compared with candesartan or enalapril (P<0.05). Brain natriuretic peptide decreased with combination therapy compared with candesartan and enalapril alone (P<0.01). Blood pressure decreased with combination therapy compared with candesartan or enalapril alone (P<0.05). Compared with enalapril, potassium levels decreased with candesartan use (P<0.05) and increased with candesartan plus enalapril (P<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality, or hospitalizations for CHF or any cause among the 3 groups.
Lee et al.[62] (2004) ARBs vs placebo (±ACE inhibitor) vs ACE inhibitor monotherapy	MA Patients with chronic heart failure and high-risk acute myocardial infarction	N=38,080 (24 trials) Duration varied	Primary: All-cause mortality and heart failure hospitalizations	Primary: ARBs were associated with reduced all-cause mortality (OR, 0.83) and heart failure hospitalizations (OR, 0.64) vs placebo. There was no difference in all-cause mortality (OR, 16) and heart failure hospitalization (OR, 0.95) between ARBs and ACE inhibitors. When ARBs were combined with ACE inhibitors, all-cause mortality was not reduced (OR, 0.97) but heart failure hospitalizations were reduced (OR, 0.77) compared to treatment with ACE inhibitors alone. Two RCT comparing ARBs with ACE inhibitors in patients with high-risk acute myocardial infarction did not reveal differences in all-cause mortality or heart failure hospitalization.
Post–Myocardial Infarction				
Pfeffer et al.[63] (2003) VALIANT Valsartan 160 mg BID	DB, MC, RCT Men and women ≥18 years with an acute myocardial infarction that was complicated by clinical or	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent myocardial	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (P=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (P=0.73).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs captopril 50 mg TID vs combination valsartan 80 mg BID and captopril 50 mg TID	radiologic signs of heart failure and/or evidence of left ventricular systolic dysfunction		infarction, hospitalization for heart failure	Secondary: The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (P=0.20). The rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (P=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash, and taste disturbance were more common in the captopril group.
Dickstein et al.[64] (2002) OPTIMAAL Losartan 50 mg QD vs captopril 50 mg TID	DB, MC, PG, RCT Patients ≥50 years (mean age 67.4 years) with an acute myocardial infarction and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18% vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; P=0.07). Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9% vs 7%; RR, 1.19; 95% CI, 0.98 to 1.43; P=0.07). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17% vs 23%; P<0.0001).
Diabetes/Diabetic Nephropathy/Renal Disease				
Mogensen et al.[65] (2000) CALM Lisinopril 20 mg QD vs	DB, DD, MC, PG, RCT Patients 30 to 75 years old with hypertension, type 2 diabetes, and microalbuminuria	N=199 24 weeks	Primary: Blood pressure and urinary albumin:creatinine ratio	Primary: At 12 weeks, mean reductions in DBP were 9.7 mm Hg (P<0.001) and 9.5 mm Hg (P<0.001), respectively, and in urinary albumin:creatinine ratio were 46% (P<0.001) and 30% (P<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (P<0.001) and 10.7 mm Hg for lisinopril alone (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
candesartan 16 mg QD vs lisinopril 20 mg QD plus candesartan 16 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.				The reduction in urinary albumin:creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; P<0.001) and candesartan alone (24%; P=0.05). All treatments were generally well tolerated.
Lewis et al.[66] (2001) IDNT Irbesartan 300 mg daily vs amlodipine 10 mg daily vs placebo	DB, MC, PC, PRO, RCT Patients 30-70 years old, with type 2 diabetes mellitus, hypertension, and nephropathy	N=1,715 2.6 years	Primary: Composite of risk of doubling serum creatinine, ESRD, or death from any cause Secondary: Composite of death from cardiovascular causes, nonfatal myocardial infarction, heart failure requiring hospitalization, permanent neurologic deficit	Primary: Compared to placebo, irbesartan 300 mg daily resulted in a 20% lower relative risk of the composite primary outcome (P=0.02). Irbesartan treatment was associated with a 33% lower risk of doubling serum creatinine (P=0.003) and 23% trend towards lower risk of ESRD (P=0.07) compared to placebo. There was no significant difference in risk of death from any cause for irbesartan compared to placebo (P=0.57). Compared to amlodipine, irbesartan treatment resulted in a 23% lower risk of composite primary outcome (P=0.006). Irbesartan treatment was associated with a 37% lower risk of doubling serum creatinine vs amlodipine (P<0.001) and 23% trend towards lower risk of ESRD vs amlodipine (P=0.07). There was no significant difference in risk of death from any cause (P=0.80). Secondary: There were no significant differences in the secondary cardiovascular composite end point (P=0.40 and P=0.79 for irbesartan vs placebo and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			caused by a cerebrovascular event, or lower limb amputation	amlodipine, respectively).
Parving et al.[67] (2001) IRMA2 Irbesartan 150 or 300 mg/day vs placebo	DB, MC, PC, RCT Patients with hypertension, type 2 diabetes mellitus and microalbuminuria	N=590 2 years	Primary: Time to onset of diabetic nephropathy Secondary: Changes in level of albuminuria and creatinine clearance and restoration of normoalbuminuria	Primary: The primary end point was reached in 5.2% of patients in the irbesartan 300 mg group (P<0.001) and 9.7% of patients in the irbesartan 150 mg group (P=0.08) compared to 14.9% of patients receiving placebo. Secondary: Irbesartan reduced the level of urinary albumin excretion by 38% in patients receiving the 300 mg dose and 24% in patients receiving the 150 mg dose vs 2% for placebo (P<0.001 for the combined irbesartan groups vs placebo and P<0.001 for the 300 vs 150 mg doses). There was no significant difference in the decline in creatinine clearance among the 3 groups. Restoration of normoalbuminuria was observed in 34% of patients receiving irbesartan 300 mg (P=0.006), 24% of patients receiving irbesartan 150 mg and 21% with placebo.
Persson et al.[106] (2009) Irbesartan 300 mg QD vs aliskiren 300 mg QD vs aliskiren 300 mg QD and irbesartan 300 mg QD	DB, XO, RCT Adults with type 2 diabetes, hypertension and albuminuria	N=26 Four 2-month treatment periods	Primary: Albuminuria (urinary albumin excretion rate) Secondary: 24-hour blood pressure and glomerular filtration rate	Primary: Treatment with aliskiren led to a significant reduction in albuminuria by 48% compared with placebo (P<0.001). Treatment with irbesartan led to a significant reduction in albuminuria by 58% compared with placebo (P<0.001). There was no significant difference in albuminuria between aliskiren and irbesartan (P value not reported). The combination of aliskiren and irbesartan significantly reduced albuminuria by 71% compared to placebo (P<0.001), which was also significantly better than with monotherapy (P<0.001 for aliskiren and P=0.028 for irbesartan). Secondary: Systolic and diastolic 24-h blood pressure were reduced by 3 mm Hg and 4 mm Hg, respectively by aliskiren (P=NS and P=0.009, respectively), 12 mm Hg and 5 mm Hg, respectively by irbesartan (P<0.001 and P=0.002, respectively), and 10 mm Hg and 6 mm Hg, respectively with the combination (P=0.001 and P <0.001, respectively) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				There was no significant change in 24-h blood pressure with irbesartan compared to combination therapy. Glomerular filtration rate was significantly reduced 4.6 ml/min/1.73 m^2 with aliskiren (P=0.037), 8.0 ml/min/1.73 m^2 with irbesartan (P<0.001), and 11.7 ml/min/1.73 m^2 with the combination (P<0.001) compared to placebo.
Bianchi et al.[104] (2010) Irbesartan 300 mg, spironolactone 25 mg, ramipril 10 mg, and atorvastatin 10 mg QD (intensive therapy) vs ramipril 10 mg and atorvastatin 10 mg QD (conventional therapy) The addition of diuretics, calcium antagonists, β-blockers or α1-receptor antagonists were added to achieve BP <130/80 mm Hg	RCT, OL Patients with a clinical diagnosis of idiopathic chronic glomerulonephritis (GN) and urine protein-creatinine ratio >1 g/g	N=128 36 months	Primary: Changes over time in proteinuria and eGFR Secondary: Adverse events and drop outs	Primary: Systolic BP decreased more in the intensive-therapy group (from 156.6 to 113.5 mm Hg) than in the conventional therapy group (from 155.7 to 122.7 mm Hg; P<0.01). Urine protein excretion decreased from 2.65 to 0.45 g/g creatinine with intensive therapy (P<0.001). With conventional therapy, urine protein excretion decreased from 2.60 to 1.23 g/g creatinine (P<0.001). With intensive therapy, eGFR did not significantly change over time (64.6 vs 62.9 mL/min/1.73 m^2). With conventional therapy, eGFR decreased from 62.5 to 55.8 mL/min/1.73 m^2 (P<0.01). Secondary: In the conventional therapy group, 8 patients discontinued the study due to hyperkalemia, cough, and rapid deterioration in kidney function. In the intensive therapy group, 15 dropped out due to hyperkalemia, cough, and hypotension. Nine patients in the intensive therapy group developed gynecomastia. Twelve patients on conventional and 31 on intensive therapy had to interrupt the study temporarily because of low BP. No patient developed an increase in creatine kinase, alanine aminotransferase, and alkaline phosphatase levels during the study.
Brenner et al.[68] (2001) RENAAL	DB, PC, RCT Patients 31-70 years of age with	N=1,513 3.4 years	Primary: Composite of risk of doubling of serum creatinine,	Primary: Compared to placebo, losartan resulted in a 16% reduction of composite primary end point (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Losartan 50 to 100 mg QD vs placebo	hypertension, type 2 diabetes mellitus and nephropathy on conventional antihypertensive therapy		ESRD, or death from any cause Secondary: Composite of morbidity and mortality from cardiovascular causes, proteinuria, rate of progression of renal disease	Losartan treatment produced a 25% reduction of doubling serum creatinine vs placebo (P=0.006) and 28% reduction in ESRD vs placebo (P=0.002). No differences in mortality were reported (P=0.88). Secondary: There was no significant difference between the losartan and placebo groups in the composite end point of morbidity and mortality from cardiovascular causes. Losartan treatment led to an average reduction in the level of proteinuria by 35% (P<0.001 vs placebo). Losartan reduced the rate of decline in renal function by 18% (P=0.01 vs placebo).
Hou et al.[69] (2007) ROAD Benazepril 10 mg/day vs individual up-titration (10 to 40 mg/day with median dose of 20 mg/day) vs losartan 50 mg/day vs individual up-titration (50 to 200 mg/day with median dose of 100 mg/day)	OL, PRO, RCT Patients aged 18-70 years with proteinuria and chronic renal insufficiency who did not have diabetes	N=360 3.7 years (median follow-up)	Primary: Time to composite of doubling of serum creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	Primary: Compared with the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through up-titration were associated with a 51% and 53% reduction in the risk for the primary end point (P=0.028 and P=0.022, respectively). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages. Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable blood pressure control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared with their conventional dosages. There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages. Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Up-titration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.				There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms.
Parving et al.[70] (2008) AVOID Losartan 100 mg daily plus aliskiren 150 mg daily for 3 months then 300 mg for an additional 3 months vs losartan 100 mg plus placebo	DB, MC, PC, RCT Hypertensive patients who were 18 to 85 years of age who had type 2 diabetes and nephropathy	N=599 6 months	Primary: Reduction in albumin:creatinine ratio at 6 months Secondary: Blood pressure reductions, adverse events	Primary: Treatment with aliskiren 300 mg daily as compared with placebo reduced the mean urinary albumin:creatinine ratio by 20% (95% CI, 9% to 30%; P<0.001), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared with 12.5% of those who received placebo (P<0.001). Secondary: A small difference in blood pressure was seen between the treatment groups by the end of the study period with SBP and DBP pressures 2 and 1 mm Hg lower, respectively, in the aliskiren group (P=0.07 and P=0.08, respectively). The total numbers of adverse and serious adverse events were similar in the groups.
Nakao et al.[115] (2003) COOPERATE Losartan 100 mg QD vs trandolapril 3 mg QD	DB, MC, PC, RCT Patients aged 18 to 70 years with chronic nephropathy (nondiabetic renal disease)	N=263 3 years	Primary: Composite of time to doubling of serum creatinine or ESRD Secondary: Changes in blood pressure, daily urinary protein excretion, adverse effects	Primary: The combined end point was reached in 11% of patients in the combination trandolapril and losartan group compared with 23% of patients in the trandolapril (P=0.018) and 23% of patients in the losartan group (P=0.016). Secondary: Mean SBP and DBP reductions were similar among the 3 treatment groups (P=0.109). All patients receiving active treatment had significant decreases in urinary protein excretion, but the greatest difference was seen with the combination trandolapril and losartan group compared to trandolapril or losartan (–75.6%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs losartan 100 mg and trandolapril 3 mg QD				–44.3% and –42.1%, respectively; P=0.01). The frequency of adverse events did not differ between groups, although a slightly higher occurrence of hyperkalemia and dry cough was recorded in the trandolapril and combination groups than in the losartan group.
Mann et al.[101] (2009) TRANSCEND Telmisartan 80 mg QD vs placebo	DB, MC, PC, RCT Adults with known cardiovascular disease or diabetes with end-organ damage but without macroalbuminuria or heart failure who cannot tolerate ACE inhibitors	N=5927 56 months	Primary: Composite outcome: first occurrence of dialysis, renal transplant, doubling of serum creatinine, or death Secondary: Changes in the estimated GFR, progression of proteinuria, and individual components of the primary outcome	Primary: The composite outcome of dialysis, doubling of serum creatinine, or death did not significantly differ between the telmisartan and placebo groups (412 patients [14.0%] vs 381 patients [12.8%]; HR, 1.10 [CI, 0.95 to 1.26]; P=0.193). The incidence of the composite outcome of dialysis or doubling of serum creatinine was similar with telmisartan and placebo (58 patients [1.96%] vs 46 patients [1.55%]; HR, 1.29 [95% CI, 0.87 to 1.89]; P=0.20). Secondary: Doubling of serum creatinine was more frequent with telmisartan than with placebo (56 vs 36 patients; P=0.031). Decreases in estimated GFR were greater with telmisartan than with placebo (mean change in estimated GFR, -3.2 ml/min per 1.73 m^2 [SD, 18.3] vs -0.26 ml/min per 1.73 m^2 [SD, 18.0]; P <0.001).
Barnett et al.[71] (2004) DETAIL Telmisartan 80 mg/day vs enalapril 20 mg/day	DB, MC, PG, RCT Patients aged 35 to 80 years with type 2 diabetes and hypertension	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in GFR, serum creatinine level, urinary albumin excretion, and blood pressure; rates of ESRD and cardiovascular events; all-cause mortality	Primary: After 5 years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, –3.0 mL/min/1.73 m^2; 95% CI, –7.6 to 1.6 mL/min/1.73m^2). Therefore, the changes in GFR were comparable between the groups. Secondary: The effects of the 2 agents on the secondary end points were not significantly different after 5 years.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Galle et al.[72] (2008) Telmisartan 80 mg QD vs valsartan 160 mg QD Additional antihypertensive therapy was allowed.	DB, MC, PG, PRO, RCT, non-inferiority study Hypertensive patients (SBP/DBP >130/80 mm Hg) with type 2 diabetes, proteinuria and serum creatinine ≤3.0 mg/dL	N=885 12 months	Primary: Change from baseline in the 24-hour proteinuria Secondary: Changes in 24-hour albuminuria, estimated GFR and inflammatory parameters	Primary: Telmisartan and valsartan produced comparable reductions in 24-hour urinary protein excretion rates: geometric mean reduction was 33% for both telmisartan and valsartan. Secondary: No significant differences between treatments were seen in changes from baseline in 24-hour urinary albumin excretion rate and GFR at 12 months. With both treatments, greater renoprotection was seen among patients with better blood pressure control. No significant changes in C-reactive protein were noted for either group at 12 months.
Fogari et al.[121] (2007) Telmisartan 40 to 160 mg and amlodipine 2.5 QD (fixed-dose combination) vs telmisartan 40 mg and amlodipine 2.5 to 10 mg QD (fixed-dose combination)	RCT, DB, MC Patients 35 to 70 years of age with essential hypertension, type 2 diabetes mellitus and microalbuminuria (UAER >30 and <300 mg/24 h	N=210 64 weeks	Primary: BP, UAER, creatinine clearance, plasma potassium, fasting glycemia, and A1C	Primary: High-dose telmisartan/low-dose amlodipine and low-dose telmisartan/high-dose amlodipine combination produced a similar reduction in systolic and diastolic BP, with no significant difference between the two regimens at any time of the study. With increasing doses of telmisartan (40 mg, 80 mg, 120 mg, and 160 mg), SBP and DBP values were reduced from baseline by 16 mm Hg and 10 mm Hg, respectively (P<0.01), 24 mm Hg and 21 mm Hg, respectively (P<0.001), 23 mm Hg and 21 mm Hg, respectively (P<0.001), and 24 mm Hg and 21 mm Hg, respectively (P<0.001). With increasing dose of amlodipine (2.5 mg, 5 mg, 7.5 mg, and 10 mg) SBP and DBP values were reduced from baseline by 16 mm Hg and 10 mm Hg, respectively (P<0.01), 25 mm Hg and 22 mm Hg, respectively (P<0.001), 25 mm Hg and 21 mm Hg, respectively (P<0.001), and 25 mm Hg and 22 mm Hg, respectively (P<0.001). Reductions of UAER from baseline were of 34.6 mg/24 h (P<0.05 vs baseline), 62.9 mg/24 h (P<0.01 vs baseline and P<0.05 vs A group), 86.5 mg/24 h (P<0.001 vs baseline and P<0.01 vs A group) and 102 mg/24 h (P<0.0001 vs baseline and P<0.001 vs A group) for telmisartan 40, 80, 120,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and 160 mg/amlodipine 2.5 mg daily, respectively. Reductions of UAER from baseline were of 35.1 mg/24 h (P<0.05 vs baseline), 46.2 mg/24 h (P<0.03 vs baseline), 50.3 mg/24 h (P<0.03 vs baseline), and 45 mg/24 h (P<0.03 vs baseline) for amlodipine 2.5, 5, 7.5, and 10 mg/telmisartan 40 mg daily, respectively. Creatinine clearance did not significantly change with either treatment. Neither combination affected levels of plasma potassium or fasting glucose. The A1C levels were not significantly influenced by either treatment.
Viberti et al.[73] (2002) MARVAL Valsartan 80 mg QD vs amlodipine 5 mg QD A target blood pressure of 135/85 mm Hg was aimed for by dose-doubling followed by the addition of bendrofluazide* and doxazosin whenever needed.	AC, DB, RCT Patients 35-75 years old with type 2 diabetes mellitus and microalbuminuria, with or without hypertension	N=332 24 weeks	Primary: Change in UAER; proportion of patients who returned to normal albuminuria Secondary: Proportion of patients returning to normoalbuminuria	Primary: Valsartan resulted in a UAER reduction of 44% at 24 weeks compared to baseline vs an 8% reduction with amlodipine (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive groups. Over the study period, blood pressure reductions were similar between the 2 treatments and at no time point was there a between-group significant difference in blood pressure values in either the hypertensive or the normotensive subgroup. Secondary: The proportion of patients returning to normal albuminuria was greater with valsartan (29.9%) vs amlodipine (14.5%; P=0.001).
Casas et al.[74] (2005) ACE inhibitor or ARBs compared	MA Studies in adults that examined the effect of any drug	127 trials 4.2 years (mean)	Primary: Doubling of serum creatinine, ESRD Secondary:	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
with placebo vs ACE inhibitor or ARBs compared with other antihypertensive drugs (β-blockers, α-adrenergic blocking agents, CCB's, or combinations) Specific agents and doses were not specified.	treatment with a blood pressure-lowering action on progression of renal disease		Serum creatinine, urine albumin excretion, GFR	A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitors or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared with other drugs, ACE inhibitors or ARBs had no effect on the GFR. Conclusion: Benefits of ACE inhibitors or ARBs on renal outcomes compared with placebo are probably due to a blood pressure-lowering effect. In diabetic patients, additional renoprotective effects of ACE inhibitors or ARBs beyond blood pressure lowering remain unproven and there is uncertainty about the greater renoprotection seen in nondiabetic renal disease.
Strippoli et al.[75] (2006) ACE inhibitors vs placebo or ARBs vs placebo or ACE inhibitors vs ARBs	MA Patients with diabetic kidney disease	N=12,067 (49 trials) Duration at least 6 months	Primary: All-cause mortality, ESRD, doubling of serum creatinine concentration, progression from micro- to macroalbuminuria, regression from micro- to normoalbuminuria, drug-related toxicity (including cough, headache,	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No statistically significant reduction in the risk of all-cause mortality was found in the 3 studies that compared ACE inhibitors with ARBs (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of studies showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98) but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to 3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBs compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hyperkalemia, impotence and pedal edema)	0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBs (RR, 0.68; 95% CI, 0.47 to 10 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively). ACE inhibitors and ARBs significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBs significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 15 to 1.93, respectively). The 7 studies that compared ACE inhibitors to ARBs did not report the outcome of ESRD or doubling of serum creatinine. Progression from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in 1 trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBs. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBs were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment.
Miscellaneous				
Papademetriou et al.[76] (2004) SCOPE Candesartan 16 mg/day vs placebo in addition to conventional	DB, MC, PC, PG, RCT Patients 70-89 years old with isolated systolic hypertension (SBP >160 mm Hg and DBP <90 mm Hg) and MMSE scores ≥24	N=1,518 3.7 years	Primary: First major coronary event including cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke Secondary: cardiovascular death, nonfatal and	Primary: There was no difference in the first major cardiovascular event between patients (with isolated systolic hypertension) who were treated with candesartan vs placebo (RR, 0.89; 95% CI, 0.65 to 1.21; P>0.20). Secondary: A total of 20 fatal/nonfatal strokes occurred in the candesartan group and 35 in the control group (RR, 0.58; 95% CI, 0.33 to 10) for a RR reduction of 42% (P=0.050 unadjusted and P=0.049 adjusted for baseline risk). There were no marked or statistically significant differences between the treatment groups in other cardiovascular end points or all-cause mortality.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy (diuretics, ACE inhibitors, β-blockers, CCBs)			fatal stroke and myocardial infarction	
Ogihara et al.[109] (2008) CASE-J Candesartan 4 to 12 mg QD vs amlodipine 2.5 to 10 mg QD	AC, MC, OL, RCT Patients with high risk hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg in patients <70 years old or SBP ≥160 mm Hg or DBP ≥90 mm Hg in patients ≥70 years old), with either type 2 diabetes, history of stroke or ischemic attack, left ventricular hypertrophy, proteinuria or serum creatinine ≥1.3 mg/dL	N=4,703 Up to 4 years	Primary: First fatal or nonfatal cardiovascular event Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events	Primary: A total of 134 patients experienced a cardiovascular event in each treatment regimen (HR, 10; 95% CI, 0.78 to 1.27; P=0.969). Secondary: All-cause death rates did not differ between treatments, 73 deaths in the candesartan group and 86 in the amlodipine group. New-onset diabetes occurred in significantly fewer patients in the candesartan group than the amlodipine group (HR, 0.64; 95% CI, 0.43 to 0.97; P=0.033). A total of 125 (5.4%) patients in the candesartan group and 134 (5.8%) of patients in the amlodipine group discontinued due to adverse events.
Taniguchi et al.[111] (2006) Candesartan 8 mg in addition to spironolactone 25 mg QD for six months, after 6 months of candesartan monotherapy (combination group)	DB, RCT, XO Patients, 67 years of age on average, with essential hypertension and left ventricular hypertrophy	N=97 1 year	Primary: Change in blood pressure and relative wall thickness	Primary: Both study groups experienced a statistically significant reduction in blood pressure from baseline (P<0.05). While candesartan was associated with a significant reduction in relative wall thickness among patients with concentric left ventricular remodeling or hypertrophy (P<0.05), the addition of spironolactone did not provide additional benefit.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs candesartan 8 mg daily for 12 months				
Montalescot et al.[103] (2009) ARCHIPELAGO Irbesartan 150 mg QD followed by 300 mg QD on day 15 vs enalapril 10 mg QD followed by 20 mg QD on day 15	DB, AC, MC, RCT Adults with non-ST elevation acute coronary syndrome	N=429 60 days	Primary: Change from baseline in high-sensitivity C-reactive protein at day 60 Secondary: Changes in other inflammatory markers such as troponin I	Primary: High-sensitivity C-reactive protein levels were comparable in both treatment groups (irbesartan: 15.2 mg/L at baseline, 6.5 mg/L at day 60; absolute change of -8.7 mg/L; enalapril: 12.6 mg/L at baseline, 5.5 mg/L at day 60; absolute change of -7.1 mg/L, P=NS). Secondary: Similarly, mean levels of markers of myocardial injury (troponin I) and endothelial dysfunction (microalbuminuria) also decreased from baseline to day 60. with no significant differences between treatment groups.
Solomon et al.[100] (2009) ALLAY Losartan 100 mg QD vs aliskiren 300 mg QD vs aliskiren 300 mg	AC, RCT Adults with hypertension and increased left ventricular wall thickness	N=465 9 months	Primary: Change in left ventricular mass	Primary: There were reductions in left ventricular mass from baseline in all treatment groups, with 4.9-g/m^2 (5.4%), 4.8-g/m^2 (4.7%), and 5.8-g/m^2 (6.4%) reductions in the aliskiren, losartan, and combination arms, respectively (P<0.0001 for all treatment groups). The reduction in left ventricular mass in the combination group was not significantly different from that with losartan alone (P=0.52). The difference in left ventricular mass regression between the aliskiren and losartan arms was within the prespecified non-inferiority margin, suggesting that aliskiren was as effective as losartan in reducing left ventricular hypertrophy (P<0.0001 for non-inferiority).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and losartan 100 mg QD				
Fliser et al.[77] (2004) EUTOPIA Olmesartan 20 mg/day and after 6 weeks, pravastatin 20 mg/day daily was added vs placebo for 6 weeks, then pravastatin 20 mg	DB, PC, PG, RCT Patients ≥18 years old with hypertension, atherosclerotic disease, type 2 diabetes mellitus, and/or LDL-C between 3.89 to 6.48 mmol/L	N=199 12 weeks	Primary: Evaluate anti-inflammatory effects of olmesartan using a panel of inflammation markers: high-sensitivity C-reactive protein, high-sensitivity tumor necrosis factor-α, interleukin-6	Primary: After 6 weeks of therapy, olmesartan treatment significantly reduced serum levels of C-reactive protein (–15.1%; P<0.05), tumor necrosis factor-α (–8.9%; P<0.02), interleukin-6 (–14.0%; P<0.05) and monocyte chemotactic protein-1 (–6.5%; P<0.01), whereas placebo treatment had no major effect on inflammation markers. After 12 weeks of therapy, C-reactive protein (–21.1%; P<0.02), tumor necrosis factor-α (–13.6%; P<0.01), and interleukin-6 (–8.0%; P<0.01) decreased further with olmesartan and pravastatin cotherapy, but treatment with pravastatin alone did not significantly alter inflammation markers. In contrast, addition of pravastatin led to a significant (P<0.001) reduction in LDL-C in the olmesartan and placebo groups (–15.1% and –12.1%, respectively).
Rosendorff et al.[118] (2009) Olmesartan 20 to 40 mg QD vs amlodipine 5 to 10 mg QD	DB, AC, RCT Adults with hypertension and left ventricular hypertrophy	N=102 52 weeks	Primary: Change in left ventricular mass from baseline to 52 weeks Secondary: Change in LV mass after 26 weeks of treatment	Primary: Mean ± SD LV masses of 252.9 ± 73.06 g in the olmesartan group and 236.9 ± 59.94 g in the amlodipine group at baseline were decreased to 248.2 ± 69.31 and 223.9 ± 53.18 g, respectively, after 52 weeks of therapy. Neither of these changes was significantly different from baseline, and the difference between the 2 treatment groups was not significant. Secondary: At 26 weeks, adjusted percent changes in LV mass were 8.0% with olmesartan and 6.0% with amlodipine. Changes occurring at the 26-week assessment were not significantly different from baseline or from each other.
ONTARGET Investigators[78] (2008) Telmisartan 80 mg/day vs	DB, MC, PC, RCT Men and women with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ	N=25,620 56 months (median follow-up)	Primary: Death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure	Primary: The primary outcome occurred in 16.5%, 16.7% and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively. Secondary: The composite of death from cardiovascular causes, myocardial infarction or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 17; P=0.001 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ramipril 10 mg/day vs ramipril 10 mg/day and telmisartan 80 mg/day	damage		Secondary: Composite of death from cardiovascular causes, myocardial infarction or stroke; heart failure, worsening or new angina, new diagnosis diabetes mellitus, new atrial fibrillation, renal impairment, revascularization procedures	non-inferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 17). There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (P<0.001 vs ramipril; no P value reported vs telmisartan). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs 4.2%; P<0.001) and angioedema (0.1% vs 0.3%; P=0.01) and a higher rate of hypotensive symptoms (2.6% vs 1.7%; P<0.001); the rate of syncope was the same in the 2 groups (0.2%). As compared with the ramipril group, combination therapy had an increased risk of hypotensive symptoms (4.8% vs 1.7%; P<0.001), syncope (0.3% vs 0.2%; P=0.03) and renal dysfunction (13.5% vs 10.2%; P<0.001).
Julius et al.[51] (2004) VALUE Valsartan 80 to 160 mg QD vs amlodipine 5 to 10 mg QD	DB, PG, RCT Patients ≥50 years old with treated or untreated hypertension and history of CVD, stroke, or diabetes, previous medications were discontinued at trial onset	N=15,245 4.2 years (mean)	Primary: Time to first cardiac event (cardiac morbidity and mortality) Secondary: Fatal and nonfatal myocardial infarction, fatal and nonfatal heart failure and fatal and nonfatal stroke, all-cause mortality, new onset diabetes	Primary: There were no differences in the primary composite end point between the valsartan and amlodipine groups (10.6% vs 10.4%; P=0.49). Secondary: There was a higher incidence of myocardial infarction (4.8% vs 4.1%; P=0.02) in patients receiving valsartan than amlodipine. There was no difference in the incidence of heart failure (4.6% vs 5.3%; P=0.12), stroke (4.2% vs 3.7%; P=0.08), and all-cause mortality (11% vs 10.8%; P=0.45) between valsartan- and amlodipine-treated patients. New onset diabetes occurred less with valsartan (13.1%) vs amlodipine (16.4%; P<0.001). Combined target blood pressure (<140/90 mm Hg) was achieved in 58% and 62% of patients receiving valsartan and amlodipine, respectively.
Sawada et al.[97] (2009)	MC, OL, BE, RCT Japanese adults with	N=3,031 Median 3.27	Primary: New onset cardiovascular or	Primary: In both groups, blood pressure was identical at baseline and at the end of study (157/88 and 133/76, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
KYOTO HEART Valsartan up to 160 mg QD plus an additional antihypertensive agent (other than an ACE inhibitor) if necessary to reach target BP <140/90 or <130/80 mm Hg vs antihypertensive agents (other than ACE inhibitors and ARBs) to reach target BP <140/90 or <130/80 mm Hg	uncontrolled hypertension and coronary artery disease, cerebral vascular disease, or peripheral vascular disease.	years	cerebrovascular events (stroke, TIA, acute MI, unstable angina, aortic aneurysm, emergency thrombosis, lower limb arterial obstruction, transition to dialysis)	The primary endpoint was recorded in fewer patients given valsartan add-on (5.5%) than in those given additional non-ARB treatment (10.2%; HR, 0.55; 95% CI, 0.42-0.72; P=0.00001). The difference in the number of primary endpoints was mainly attributable to reduced frequency of stroke and TIA, and unstable angina. These benefits cannot be explained by a difference in blood pressure control.
The GISSI-AF Investigators[99] (2009) GISSI-AF Valsartan up to 320 mg QD vs placebo	MC, DB, PC, RCT Adults in sinus rhythm who had a recent history of documented atrial fibrillation	N=1,442 1 year	Primary: Time to a first occurrence of atrial fibrillation and proportion of patients who had more than one recurrence of atrial fibrillation over the course of 1 year	Primary: Atrial fibrillation recurred in 371 of the 722 patients (51.4%) in the valsartan group, as compared with 375 of 720 (52.1%) in the placebo group (adjusted hazard ratio, 0.97; 96% CI, 0.83 to 1.14; P=0.73). More than one episode of atrial fibrillation occurred in 194 of 722 patients (26.9%) in the valsartan group and in 201 of 720 (27.9%) in the placebo group (adjusted odds ratio, 0.89; 99% CI, 0.64 to 1.23; P=0.34).
The Navigator Study Group[102] (2010)	DB, MC, RCT Adults with	N=9,306 5 years	Primary: Incidence of diabetes and a	Primary: The cumulative incidence of diabetes was 33.1% in the valsartan group, as compared with 36.8% in the placebo group (hazard ratio in the valsartan

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
NAVIGATOR Valsartan up to 160 mg QD or matching placebo and nateglinide or matching placebo	impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors.		composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina	group, 0.86; 95% Cl, 0.80 to 0.92; P<0.001). Valsartan, as compared with placebo, did not significantly reduce the incidence of the composite cardiovascular outcome (14.5% vs 14.8%; hazard ratio, 0.96; 95% Cl, 0.86 to 17; P=0.43).
Blood Pressure Lowering Treatment Trialists' Collaboration[53] (2007) ACE inhibitors vs ARBs	MA Patients with high blood pressure, diabetes, history of CHD or cerebrovascular disease	N=146,838 (26 trials) Duration varied	Primary: Nonfatal myocardial infarction or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease	Primary: From a total of 146,838 individuals with high blood pressure or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable blood pressure-dependent reductions in risk with ACE inhibitors and ARBs (P≥0.3 for all 3 outcomes). ACE inhibitors produced a blood pressure-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3% to 14%). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard (P=0.002). For both stroke and heart failure, there was no evidence of any blood pressure-independent effects of either ACE inhibitors or ARBs.

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: AC=active comparator, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ABPM=ambulatory blood pressure monitoring, ARB=angiotensin II receptor antagonist, β-blockers=β-adrenergic blocking agents, BE=blinded endpoint, CAD=coronary artery disease, CCBs=calcium-channel blocking agents, CHD=coronary heart disease, CHF=congestive heart failure, DBP=diastolic blood pressure, ESRD=end-stage renal disease, GFR=glomerular filtration rate, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, LVH=left ventricular hypertrophy, MAP=mean arterial pressure, MMSE=Mini Mental State Examination, NYHA=New York Heart Association, SBP=systolic blood pressure, UAER=urinary albumin excretion rate, WMD=weighted mean difference

Additional Evidence

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

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

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

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For 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 12. Relative Cost of the Angiotensin II Receptor Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Candesartan	tablet	Atacand®	$$$-$$$$	N/A
Candesartan and hydrochlorothiazide	tablet	Atacand HCT®	$$$	N/A
Eprosartan	tablet	Teveten®	$$$-$$$$	N/A
Eprosartan and hydrochlorothiazide	tablet	Teveten HCT®	$$$	N/A
Irbesartan	tablet	Avapro®	$$$	N/A
Irbesartan and hydrochlorothiazide	tablet	Avalide®	$$$	N/A
Losartan	tablet	Cozaar®*	$$$	$$-$$$
Losartan and hydrochlorothiazide	tablet	Hyzaar®*	$$$	$$$
Olmesartan	tablet	Benicar®	$$$	N/A
Olmesartan and hydrochlorothiazide	tablet	Benicar HCT®	$$$	N/A
Telmisartan	tablet	Micardis®	$$$	N/A
Telmisartan and amlodipine	tablet	Twynsta®	$$$$	N/A
Telmisartan and hydrochlorothiazide	tablet	Micardis HCT®	$$$	N/A
Valsartan	tablet	Diovan®	$$$	N/A
Valsartan and hydrochlorothiazide	tablet	Diovan HCT®	$$$-$$$$	N/A

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

X. Conclusions

All of the angiotensin II receptor blockers (ARBs) are approved for the treatment of hypertension.[1-18] Some of the products are also approved for the treatment of diabetic nephropathy (irbesartan and losartan), heart failure (candesartan and valsartan), post-myocardial infarction (valsartan), as well as cardiovascular and cerebrovascular risk reduction (telmisartan and losartan, respectively). The ARBs are available as single entity products, as well as in combination with hydrochlorothiazide. Telmisartan is also available in combination with amlodipine. There are other ARBs that are available in combination with amlodipine (olmesartan and valsartan); however, these products are included in the dihydropyridines class review (AHFS Class 242808). Losartan and losartan/hydrochlorothiazide are the only ARBs available in a generic formulation.

National and international guidelines recommend the use of ACE inhibitors or ARBs in patients with cerebrovascular disease, coronary artery disease, heart failure, hypertension, left ventricular dysfunction, left ventricular hypertrophy, diabetes, diabetic nephropathy, previous myocardial infarction and renal disease.[23-40,107] Some of the guidelines specifically recommend the use of ACE inhibitors as initial therapy, with the subsequent use of ARBs in patients who do not tolerate ACE inhibitors.[24,28-30,38-40] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[31-32,34-37] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, ARBs and β-blockers do not differ in their ability to reduce blood pressure.[35,107] There is no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[35,107] Guidelines recommend that the selection of an antihypertensive agent be based on compelling indications for use.[31-37,107]

Numerous clinical trials have shown that the ARBs can effectively lower systolic and diastolic blood pressure, administered alone or in combination with other antihypertensive agents.[42,65,80-82,84-92,94-96,98,108,113-114,116-117,119-120,122-123] Some comparative trials have demonstrated slight differences in blood pressure effects among the various ARBs; however, the clinical significance of these differences remains to be established.[42,48-49,80,84,87,94-96] Guidelines do not give preference to one ARB over another for the treatment of hypertension.[31-37,107] Most patients will require more than one antihypertensive agent to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[35,107] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

ARBs have been shown to reduce cardiovascular morbidity and mortality, as well as preserve renal function.[4,8,10-11,14,17,54-57,66-68,72-73,106,121] The use of losartan also decreases the risk of stroke in patients with hypertension and left ventricular hypertrophy.[10-11] It should be noted that the ACE inhibitors have also been shown to positively impact these endpoints as well (please refer to ACE inhibitor class review for additional information). Several studies comparing ARBs and ACE inhibitors have demonstrated similar efficacy with regards to cardiovascular events, heart failure and the rate of progression of nephropathy.[55,59-64,66,68-69,71,75,78,115] ACE inhibitors inhibit the breakdown of bradykinin, which may lead to the development of a persistent non-productive cough. The ARBs do not increase bradykinin and may be better tolerated in some patients.

The FDA is evaluating data from two clinical trials (ROADMAP and ORIENT) in which patients with type 2 diabetes who were taking olmesartan had a higher rate of death from cardiovascular causes compared to those who were taking placebo.[124] The FDA's review is ongoing and no conclusions have been made. However, the FDA currently believes that the benefits of using olmesartan in patients with hypertension outweigh the potential risks. A meta-analysis, which combined cancer-related findings from several clinical trials, suggested that the use of ARBs may be associated with a small increased risk of cancer.[125] The meta-analysis included data from over 60,000 patients with a mean follow-up of 1.7-4.8 years. The rate of cancer occurrence in those taking an ARB was 7.2% compared to 6.0% in those not taking an ARB (RR, 1.08; 95% CI, 1.01-1.15). The FDA has not concluded that ARBs increase the risk of cancer, and they believe that the benefits of ARBs continue to outweigh their potential risks.

At this time, there is insufficient evidence to conclude that the angiotensin II receptor antagonists offer a significant clinical advantage over other alternatives in general use. Therefore, all brand angiotensin II receptor antagonists 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 angiotensin II receptor antagonist 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 Mineralocorticoid (Aldosterone) Receptor Antagonists
AHFS Class 243220
November 10, 2010

I. Overview

Aldosterone is a component of the renin-angiotensin-aldosterone (RAAS) system, which is responsible for the regulation of extracellular volume and blood pressure. Upon binding to the mineralocorticoid receptor on the distal renal tubule, aldosterone activates the sodium-potassium exchange pump, leading to sodium and water retention, as well as potassium excretion. Increased levels of aldosterone are present in both primary and secondary hyperaldosteronism.[5] Heart failure, hepatic cirrhosis and the nephrotic syndrome are edematous conditions, which can lead to secondary aldosteronism. Volume depletion and sodium loss due to diuretic therapy may also cause secondary aldosteronism.[5]

The mineralocorticoid (aldosterone) receptor antagonists are approved for the treatment of edema, heart failure, hypertension, hypokalemia and primary hyperaldosteronism.[1-6] Eplerenone and spironolactone bind to mineralocorticoid receptors, which blocks the binding of aldosterone. They are available as single entity agents, and spironolactone is also available in combination with hydrochlorothiazide. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.

The mineralocorticoid (aldosterone) receptor antagonists 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 September 2008.

Table 1. Mineralocorticoid (Aldosterone) Receptor Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Eplerenone	tablet	Inspra®*	eplerenone
Spironolactone	tablet	Aldactone®*	spironolactone
Spironolactone and hydrochlorothiazide	tablet	Aldactazide®*	spironolactone and hydrochlorothiazide

*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 mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 2. For a comprehensive overview of the pharmacologic management of acute myocardial infarction, heart failure, and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Mineralocorticoid (Aldosterone) Receptor Antagonists

Clinical Guideline	Recommendation(s)
European Society of Cardiology (ESC): **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation[9] (2008)**	Secondary Prevention • Aldosterone blockade may be considered for post-STEMI patients with an EF <40% and heart failure or diabetes provided that creatinine is <2.5 mg/dL in men and <2.0 mg/dL in women, and potassium is ≤5.0 mEq/L.
American College of Cardiology (ACC)/ American Heart Association (AHA): **2007 Focused Update of the**	Secondary Prevention • Use of aldosterone blockade in post-MI patients without significant renal dysfunction or hyperkalemia is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and β-blocker,

Clinical Guideline	Recommendation(s)
ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (STEMI)[7] (2007)	have an LVEF of ≤40%, and have either diabetes or HF.
National Institute for Health and Clinical Excellence (NICE): **Post Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction[8] (2007)**	Secondary Prevention • For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment should be initiated within 3–14 days of the MI, preferably after ACE inhibitor therapy.
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[67] (2007)**	• Aldosterone blockade is recommended 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 left ventricular ejection fraction ≤40% and have either diabetes or heart failure.
American College of Cardiology (ACC)/American Heart Association (AHA): **2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[68] (2007)**	Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge • Aldosterone blockers should be initiated in patients without significant renal dysfunction or hyperkalemia who are receiving therapeutic doses of an ACE inhibitor, have a left ventricular ejection fraction <40%, and either symptomatic heart failure or diabetes.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)[62] (2007)**	Long-term Management • Aldosterone antagonists should be considered in patients who are already on an ACE inhibitor and β-blocker after an MI, who have a left ventricular ejection fraction of ≤40%, diabetes, or heart failure and who do not have significant renal dysfunction or hyperkalemia.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline[11] (2010)**	Patients With Left Ventricular Systolic Dysfunction • Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. • Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. • The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF • ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended.

Clinical Guideline	Recommendation(s)
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**[10] **(2009)**	Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Aldosterone antagonists may be beneficial in patients with moderately severe-to-severe symptoms of heart failure with reduced left ventricular ejection fraction, though careful monitoring is required. • The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[12] **(2008)**	Pharmacologic Therapy of Chronic Heart Failure • Aldosterone antagonist should be considered in all patients with an LVEF ≤35% and severe symptomatic heart failure (NYHA class III-IV) in the absence of hyperkalemia and significant renal dysfunction, unless contraindicated or not tolerated. Patients should also be receiving ACE inhibitor (or ARB) and β-blocker therapy.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management**[62] **(2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension**[15] **(2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation

Clinical Guideline	Recommendation(s)
	(β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[16] (2006)**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[13] (2004)**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs, or CCBs. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-MI (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor).

Clinical Guideline	Recommendation(s)
	• For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2-4 times higher in African American patients. • Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should not be used in patients whose potassium levels are greater than 5.0 mEq/L.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[20] (2004)**	• ACE inhibitors and ARBs have many advantages for patients with chronic kidney disease (CKD) and associated comorbid medical conditions. They slow the progression of diabetic kidney disease and nondiabetic kidney disease with proteinuria, and in addition, they reduce proteinuria, irrespective of the type of kidney disease. • ACE inhibitors are more effective than other antihypertensive agents in slowing the progression of most nondiabetic kidney diseases. The beneficial effect is greater in patients with severe proteinuria. • ARBs may be more effective than other antihypertensive agents in slowing the progression of nondiabetic kidney disease. • ACE inhibitors and ARBs in combination may be more effective than either alone in slowing the progression of nondiabetic kidney disease. • Diuretics may potentiate the beneficial effects of ACE inhibitors and ARBs in nondiabetic kidney disease. • ACE inhibitors, ARBs, and nondihydropyridine calcium-channel blockers have a greater antiproteinuric effect than other antihypertensive classes in nondiabetic kidney disease. • Dihydropyridine calcium-channel blockers are less effective than other agents in slowing the progression of nondiabetic kidney disease with proteinuria. • The K/DOQI guidelines do not address the use of aldosterone receptor antagonists for the management of nondiabetic kidney disease.
World Health Organization (WHO)/International Society of Hypertension (ISH): **WHO/ISH Statement on Management of Hypertension[14] (2003)**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular

Clinical Guideline	Recommendation(s)
	dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors). • No specific recommendation is made concerning combination mineralocorticoid (aldosterone) receptor antagonists.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans[19] (2003)**	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • No specific recommendation is made concerning the mineralocorticoid (aldosterone) receptor antagonists.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[18] (2010)**	• Multiple drug therapy is generally required to achieve blood pressure goals. • No specific recommendation is made concerning the mineralocorticoid (aldosterone) receptor antagonists.
American Association for the Study of Liver Diseases (AASLD): **Management of Adult Patients with Ascites Due to Cirrhosis: An Update[22] (2009)**	• First-line treatment of patients with cirrhosis and ascites consists of sodium restriction and diuretics (oral spironolactone with or without oral furosemide). Spironolactone monotherapy may be used only in patients who have minimal fluid overload. • In patients experiencing painful gynecomastia with spironolactone, amiloride may be an appropriate substitute. However, amiloride has been shown to be less effective than an active metabolite of spironolactone. • Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites. Hydrochlorothiazide can also cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses.
World Gastroenterology Organization (WGO) Practice Guideline: **Management of Ascites Complicating Cirrhosis in Adults[23]**	• Initial oral diuretic therapy consists of single daily doses of spironolactone or spironolactone in addition to furosemide. • Spironolactone monotherapy is more effective compared to furosemide monotherapy. However its use should be restricted to patients exhibiting minimal fluid overload. • Spironolactone monotherapy may be complicated by hyperkalemia and gynecomastia. Amiloride and triamterene are substitutes for spironolactone. • Indications of diuretic resistance include minimal to no weight loss and urinary sodium excretion of <78 mmol/day. Diuretic therapy should be discontinued in patients who develop encephalopathy, clinically significant complications of diuretics, hyperkalemia, metabolic acidosis with spironolactone, and whose serum sodium is <120 mmol/L or serum creatinine >2 mg/dL.
Endocrine Society (ES): **Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism[66] (2008)**	• For patients with documented unilateral primary aldosteronism, treatment by unilateral laparoscopic adrenalectomy is recommended. • Medical treatment with a mineralocorticoid receptor antagonist is recommended for patients who cannot or who do not wish to undergo surgery. • Medical treatment with a mineralocorticoid receptor antagonist is recommended for patients with primary aldosteronism caused by bilateral adrenal disease. Spironolactone is suggested as the primary agent, with eplerenone as an alternative.

Clinical Guideline	Recommendation(s)
	• Use of the lowest dose of glucocorticoid that can normalize blood pressure and serum potassium levels is recommended in patients with glucocorticoid-remediable aldosteronism, rather than first-line treatment with a mineralocorticoid receptor antagonist.
American Association of Clinical Endocrinologists (AACE): **Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Hypertension**[21] **(2006)**	Primary Hyperaldosteronism • Surgery is the preferred treatment modality for patients with unilateral adenomas. • Spironolactone may be used in lieu of surgery in female or elderly patients with small adenomas or hyperplasias. Since male patients may experience erectile dysfunction and gynecomastia with spironolactone therapy, a trial of eplerenone may be considered. • Glucocorticoid-remediable aldosteronism is treated with glucocorticoids.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the mineralocorticoid (aldosterone) receptor antagonists 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 Mineralocorticoid (Aldosterone) Receptor Antagonists[1-6]

Indication	Eplerenone	Spironolactone	Spironolactone/ Hydrochlorothiazide
Edema			
For the management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of, other therapeutic measures		✔	✔
Heart Failure			
For patients with congestive heart failure taking digitalis when other therapies are considered inappropriate		✔	✔
For the treatment of diuretic-induced hypokalemia in patients with congestive heart failure when other measures are considered inappropriate			✔
For patients with severe heart failure (NYHA class III – IV) to increase survival, and to reduce the need for hospitalization for heart failure when used in addition to standard therapy		✔	
To improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction	✔		
Hypertension			
Treatment of hypertension	✔ *		
Treatment of hypertension for patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate		✔	✔

Indication	Eplerenone	Spironolactone	Spironolactone/ Hydrochlorothiazide
Hypokalemia			
For the prophylaxis of hypokalemia in patients taking digitalis when other measures are considered inadequate or inappropriate		✔	
For the treatment of patients with hypokalemia when other measures are considered inappropriate or inadequate		✔	
For the treatment of a diuretic-induced hypokalemia in hypertensive patients when other measures are considered inappropriate			✔
Primary Hyperaldosteronism			
To establish the diagnosis of primary hyperaldosteronism by therapeutic trial		✔	
Short-term preoperative treatment of patients with primary hyperaldosteronism		✔	
Long-term maintenance therapy for patients with discrete aldosterone-producing adrenal adenomas who are judged to be poor operative risks or who decline surgery		✔	
Long-term maintenance therapy for patients with bilateral micro or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism)		✔	
Miscellaneous			
For nephrotic patients when treatment of the underlying disease, restriction of fluid and sodium intake, and the use of other diuretics do not provide an adequate response		✔	✔
For treatment of patients with cirrhosis of the liver (accompanied by edema and/or ascites) for maintenance therapy together with bed rest and the restriction of fluid and sodium		✔	✔

*Alone or in combination with other antihypertensive agents.

IV. Pharmacokinetics

The pharmacokinetic parameters of the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Eplerenone	69	50	Liver Kidney	Renal (67) Feces (32)	4-6
Spironolactone	73	90	Liver Kidney	Renal (47-57) Feces (35-41)	1.3-1.4
Spironolactone and hydrochlorothiazide	H: 60-80 S: 73	H: 40 S: 90	S: Liver Kidney	H: Renal (50-70) S: Renal (47-57) Feces (35-41)	H: 4-5 S: 1.3-1.4

H=hydrochlorothiazide, S=spironolactone

V. Drug Interactions

Significant drug interactions with the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 5.

Table 5. Significant Drug Interactions with the Mineralocorticoid (Aldosterone) Receptor Antagonists[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Aldosterone blockers (eplerenone, spironolactone, spironolactone-hydrochlorothiazide)	1	ACE Inhibitors	Serious hyperkalemia, possibly with cardiac arrhythmias or arrest, may occur with the combination of aldosterone blockers and ACE inhibitors. Potassium sparing effects are additive when combining ACE inhibitors with aldosterone blockers. Aldosterone acts in the renal cortical collecting ducts by inducing synthesis of proteins that constitute the Na+, K+-ATPase pump. The pump acts to reabsorb sodium and water in exchange for potassium, which is then eliminated in the urine. Aldosterone antagonism can cause hyperkalemia.
Aldosterone blockers (eplerenone, spironolactone, spironolactone-hydrochlorothiazide)	1	Amiloride	Aldosterone blockers and amiloride may exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result. Aldosterone blockers and amiloride may cause additive adverse effects when co-administered.
Aldosterone blockers (eplerenone, spironolactone, spironolactone-hydrochlorothiazide)	1	Potassium Preparations	Potassium preparations will increase serum potassium concentrations. This may increase the potential for clinically important hyperkalemia, especially when used concomitantly with aldosterone blockers.
Aldosterone blockers (eplerenone, spironolactone, spironolactone-hydrochlorothiazide)	1	Triamterene	Eplerenone and triamterene may exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result.
Eplerenone	1	HIV Protease Inhibitors	Inhibition of cytochrome P450 3A4 isoenzymes by HIV protease inhibitors may decrease the metabolic elimination of aldosterone blockers. HIV protease inhibitors may increase plasma concentrations and pharmacologic or toxic effects of aldosterone blockers.
Eplerenone	1	Imidazoles	Certain azole antifungal agents may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased

Generic Name(s)	Significance Level	Interaction	Mechanism
			concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone.
Eplerenone	1	Macrolides	Macrolides may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone.
Eplerenone	1	Nefazodone	Nefazodone may decrease the elimination of eplerenone by inhibiting its hepatic metabolism via CYP3A4 isoenzyme resulting in increased concentration and consequently increased pharmacologic and toxic (hyperkalemia associated with potentially fatal arrhythmias) effects of eplerenone. Coadministration of eplerenone with nefazodone is contraindicated.
Eplerenone	1	Spironolactone	Eplerenone and spironolactone may exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Spironolactone	1	Angiotensin II Receptor Antagonists	Decreased aldosterone activity by angiotensin II receptor antagonists may function synergistically with potassium conservation by spironolactone to produce substantial hyperkalemia. The risk of hyperkalemia may be increased when spironolactone is co-administered with angiotensin II receptor antagonists.
Eplerenone	2	Verapamil	Inhibition of cytochrome P450 3A4 isoenzymes by verapamil may decrease the metabolic elimination of eplerenone. Verapamil may increase plasma concentrations and pharmacologic or toxic effects of eplerenone.
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with

Generic Name(s)	Significance Level	Interaction	Mechanism
			a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided. When used together, blood and urine glucose levels should be frequently monitored, and dosage reductions may be required.
Hydrochlorothiazide	2	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium-sparing diuretics to prevent further losses.
Spironolactone	2	Aliskiren	Decreased aldosterone activity by aliskiren may function synergistically with potassium conservation by spironolactone leading to the development of hyperkalemia. The risk of hyperkalemia may be increased when aliskiren is coadministered with spironolactone.
Spironolactone	2	Macrolide Immunosuppressives	Macrolide immunosuppressives and spironolactone may exert additive effects on potassium leading to hyperkalemia.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 6. The boxed warning for the mineralocorticoid (aldosterone) receptor antagonists are listed in Tables 7 – 8.

Table 6. Adverse Drug Events (%) Reported with the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-6]

Adverse Events	Eplerenone	Spironolactone	Spironolactone/ Hydrochlorothiazide
Cardiovascular			
Orthostatic hypotension	-	-	✔
Central Nervous System			
Ataxia	-	✔	✔
Confusion	-	✔	✔
Dizziness	3	-	✔
Drowsiness	-	✔	✔
Fatigue	2	✔	✔
Fever	-	✔	✔
Headache	-	✔	✔
Insomnia	-	-	✔

Adverse Events	Eplerenone	Spironolactone	Spironolactone/ Hydrochlorothiazide
Lethargy	-	✔	✔
Restlessness	-	-	✔
Vertigo	-	-	✔
Dermatological			
Alopecia	-	-	✔
Cutaneous vasculitis	-	-	✔
Erythema multiforme	-	-	✔
Exfoliative dermatitis	-	-	✔
Maculopapular eruptions	-	-	✔
Necrotizing angiitis	-	-	✔
Photosensitivity	-	-	✔
Pruritus	-	-	✔
Purpura	-	-	✔
Rash	<1	✔	✔
Stevens-Johnson syndrome	-	-	✔
Toxic epidermal necrolysis	-	-	✔
Urticaria	-	✔	✔
Endocrine and Metabolic			
Amenorrhea	-	✔	✔
Breast cancer	-	✔	✔
Deepening of the voice	-	✔	✔
Dehydration	-	✔	✔
Gynecomastia	≤1	9	9
Hyperchloremic metabolic acidosis	-	✔	✔
Irregular menses	-	✔	✔
Mastodynia	≤1	2	2
Postmenopausal bleeding	-	✔	✔
Gastrointestinal			
Abdominal pain	1	-	✔
Anorexia	-	✔	✔
Cholestatic toxicity	-	✔	✔
Constipation	-	-	✔
Cramping	-	✔	✔
Diarrhea	2	✔	✔
Gastritic bleeding	-	✔	✔
Gastritis	-	✔	✔
Nausea	-	✔	✔
Pancreatitis	-	-	✔
Sialoadenitis	-	-	✔
Ulceration	-	✔	✔
Vomiting	-	✔	✔
Xerostomia	-	✔	✔
Genitourinary			
Abnormal vaginal bleeding	≤2	-	-
Albuminuria	1	-	-
Glucosuria	-	-	✔
Impotence	-	✔	✔
Interstitial nephritis	-	-	✔
Renal dysfunction	-	✔	✔
Renal failure	-	✔	✔
Hematologic			
Agranulocytosis	-	✔	✔
Aplastic anemia	-	-	✔

Adverse Events	Eplerenone	Spironolactone	Spironolactone/ Hydrochlorothiazide
Eosinophilia	-	✔	✔
Hemolytic anemia	-	-	✔
Leukopenia	-	-	✔
Thrombocytopenia	-	-	✔
Laboratory Test Abnormalities			
Blood urea nitrogen increased	<1	✔	✔
Creatinine increased	6	-	-
Hypercholesterolemia	≤1	-	-
Hyperglycemia	-	-	✔
Hyperkalemia	≤32	≤40	≤40
Hypertriglyceridemia	<15	-	-
Hyponatremia	2	✔	✔
Hyperuricemia	<1	-	✔
Liver function tests increased	<1	-	-
Respiratory			
Cough	2	-	-
Respiratory distress	-	-	✔
Other			
Anaphylaxis	-	✔	✔
Angioneurotic edema	<1	-	-
Blurred vision	-	-	✔
Flu-like syndrome	2	-	-
Hepatocellular toxicity	-	✔	✔
Jaundice	-	-	✔
Muscle cramps	-	-	✔
Vasculitis	-	✔	✔
Weakness	-	-	✔
Xanthopsia	-	-	✔

✔ Percent not specified
\- Event not reported

Table 7. Boxed Warning for Spironolactone[1]

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Use spironolactone only in those conditions for which it is indicated. Avoid unnecessary use of this drug.

Table 8. Boxed Warning for Spironolactone/Hydrochlorothiazide[1]

WARNING
Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see Precautions). Aldactazide should be used only in those conditions described under Indications and Usage. Unnecessary use of this drug should be avoided. Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static but must be reevaluated as conditions in each patient warrant.

VII. Dosing and Administration

The usual dosing regimens for the mineralocorticoid (aldosterone) receptor antagonists are listed in Table 9.

Table 9. Usual Dosing Regimens for the Mineralocorticoid (Aldosterone) Receptor Antagonists[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Eplerenone	Heart Failure: Initial, 25 mg once daily for 4 weeks; maintenance, 50 mg once daily Hypertension: Initial, 50 mg once daily; maximum, 50 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg
Spironolactone	Edema (Congestive Heart Failure, Hepatic Cirrhosis, Nephrotic Syndrome): Initial: 100 mg once daily in single or divided doses; maintenance, 25 to 200 mg once daily Heart Failure (Severe, NYHA Class III-IV) Initial: 25 mg once daily; maintenance, 25 mg every other day to 50 mg once daily Hypertension Initial: 50 to 100 mg once daily in single or divided doses; maintenance, 25 to 200 mg once daily; maximum, 400 mg daily Hypokalemia: 25 to 100 mg once daily Primary Hyperaldosteronism (Diagnosis): Long test: 400 mg daily for 3 to 4 weeks Short test: 400 mg daily for 4 days Primary Hyperaldosteronism-(Short-term Preoperative Therapy): 100 to 400 mg daily prior to surgery Primary Hyperaldosteronism-(Long-term Maintenance Therapy): Initial: 100 to 400 mg daily; maximum, 400 mg daily	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Spironolactone and hydrochlorothiazide	Edema (Congestive Heart Failure, Hepatic Cirrhosis, Nephrotic Syndrome): Maintenance: 100 mg-100 mg administered daily in single or divided doses; may range from 25 mg-25 mg to 200 mg-200 mg daily Hypertension: Maintenance: 50 mg-50 mg to 100 mg-100 mg daily in single or divided doses	Safety and efficacy in children have not been established.	Tablet: 25 mg-25 mg 50 mg-50 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the mineralocorticoid (aldosterone) receptor antagonists are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Mineralocorticoid (Aldosterone) Receptor Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Heart Failure				
Pitt et al.[28] (2003) EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	DB, MC, RCT Patients with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure)	N=6,632 16 months	Primary: Death from any cause, composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event (including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia) Secondary: Death from any cause or any hospitalization, death from cardiovascular causes, any hospitalization, hospitalization for cardiovascular causes, hospitalization for heart failure, adverse events	Primary: Significantly less patients in the eplerenone group died from any cause compared to those receiving placebo (478 vs 554; RR, 0.85; 95% CI, 0.75 to 0.96; P=0.008). Significantly fewer patients in the eplerenone group died from or required hospitalization for cardiovascular events compared to those receiving placebo (885 vs 993; RR, 0.87; 95% CI, 0.79 to 0.95; P=0.002). Secondary: Significantly fewer patients in the eplerenone group died from any cause or required hospitalization compared to those receiving placebo (1,730 vs 1,829; RR, 0.92; 95% CI, 0.86 to 0.98; P=0.02). Death from cardiovascular causes was 12.3% in the eplerenone group and 14.6% in the placebo group (RR, 0.83; 95% CI, 0.72 to 0.94; P=0.005.) Fewer patients in the eplerenone group required hospitalization compared to those receiving placebo (1,493 vs 1,526; RR, 0.95; 95% CI, 0.89 to 12; P=0.2); however the difference was not statistically significant. Fewer patients in the eplerenone group required hospitalization due to a cardiovascular event compared to those receiving placebo (606 vs 649; RR, 0.91; 95% CI, 0.81 to 11; P=0.09); however the difference was not statistically significant. There was a relative reduction of 15% in the risk of hospitalization for heart failure in the eplerenone group (RR, 0.85; P=0.03) and 23% fewer episodes of hospitalization for heart failure were reported in the eplerenone group compared to the placebo group (RR, 0.77; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Serious hyperkalemia (serum potassium ≥6.0 mmol/L) occurred in 5.5% of the eplerenone-treated patients compared to 3.9% of patients in the placebo group (P=0.002). The incidence of hyperkalemia was higher among those with a lower baseline creatinine clearance (P<0.001). At one year, the serum creatinine concentration had increased by 0.02 mg/dL in the placebo group and by 0.06 mg/dL in the eplerenone group (P<0.001). There were no significant differences between eplerenone and placebo in the incidence of sex hormone-related adverse events, including gynecomastia, impotence, breast pain, and abnormal vaginal bleeding (P>0.05).
Pitt et al.[29] (2005) EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	DB, MC, RCT (post-hoc analysis) Patients with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure)	N=6,632 30 days	Primary: Death from any cause, and composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event at 30 days Secondary: Death from cardiovascular causes, sudden cardiac death, fatal or nonfatal heart failure hospitalization, adverse events	Primary: A significantly lower percentage of patients in the eplerenone group died from any cause compared to those receiving placebo (3.2% vs 4.6%; P=0.004). A lower percentage of patients in the eplerenone group died from or required hospitalization for cardiovascular events compared to those receiving placebo (8.6% vs 9.9%; P=0.074); however, the difference was not statistically significant. Secondary: A significantly lower percentage of patients in the eplerenone group died from cardiovascular cause compared to those receiving placebo (3.0% vs 4.4%; P=0.003). A lower incidence of sudden cardiac death was noted among patients in the eplerenone group compared to those receiving placebo (0.9% vs 1.4%; P=0.051); however, the difference was not statistically significant. A lower percentage of patients in the eplerenone group required hospitalization for fatal/nonfatal heart failure compared to those receiving placebo (3.4% vs 4.2%; P=0.106); however, the difference was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no statistically significant difference between eplerenone and placebo in the number of patients experiencing at least 1 adverse event during 30-day therapy (P=0.29). At 30 days, the serum potassium concentration had increased by 0.17 mmol/L in the placebo group and by 0.24 mmol/L in the eplerenone group (P<0.001).
Pitt et al.[30] (2006) EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	DB, MC, RCT (post-hoc analysis of patients with LVEF ≤30%) Patients with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure)	N=2,106 16 months	Primary: Death from any cause, and composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event Secondary: Death from cardiovascular causes, sudden cardiac death, a composite endpoint of heart failure death and heart failure hospitalizations	Primary: Eplerenone was associated with a significant 21% reduction in the risk of all-cause mortality compared to placebo (P=0.012). Eplerenone was associated with a significant reduction in the risk of the composite endpoint of death from cardiovascular causes or hospitalization for a cardiovascular event compared to placebo (P=0.001). Secondary: Eplerenone was associated with a significant 23% reduction in the risk of cardiovascular mortality compared to placebo (P=0.008). The relative risk of sudden cardiac death was reduced by 33% (P=0.01) and heart failure mortality/heart failure hospitalization composite endpoint was reduced by 25% (P=0.005) with eplerenone compared with placebo. At 30 days, eplerenone was associated with relative risk reductions of 43% for all-cause mortality (P=0.002), 29% for cardiovascular mortality/cardiovascular hospitalization composite endpoint (P=0.006), and 58% for sudden cardiac death (P=0.008).
O'Keefe et al.[31] (2007) EPHESUS Eplerenone 25 mg daily for 4 weeks,	DB, MC, RCT (post-hoc analysis of patients with diabetes) Patients with acute myocardial	N=1,483 16 months	Primary: Death from any cause, and composite endpoint of death from cardiovascular	Primary: Eplerenone was not associated with a significant reduction in the risk of all-cause mortality compared to placebo (P=0.131). Eplerenone treatment in diabetic patients was associated with a significant 17% reduction in the risk of death from cardiovascular causes or hospitalization for a cardiovascular event compared to placebo (P=0.031).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by titration to 50 mg daily vs placebo Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure)		causes or hospitalization for a cardiovascular event Secondary: Death from cardiovascular causes, sudden cardiac death, hyperkalemia	Secondary: Eplerenone was not associated with a significant reduction in the risk of cardiovascular mortality compared to placebo (P=0.128). Eplerenone was not associated with a significant reduction in the risk of sudden cardiac death compared to placebo (P=0.533). Eplerenone was associated with a greater incidence of hyperkalemia compared to placebo (5.6% vs 3%; P=0.015).
Gheorghiade et al.[58] (2009) EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-	DB, MC, RCT (post-hoc analysis) Patients with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure)	N=6,632 16 months	Primary: Mean length of stay per episode of heart failure hospitalization and the total number of days of heart failure hospitalizations	Primary: Eplerenone was associated with a significant reduction in the mean length of hospital stay per episode of HF hospitalization of 1.6 days (9.2 vs 10.8 days with placebo; P=0.019). Treatment with eplerenone was associated with a reduction in the total number of days of HF hospitalization per patient of 3.6 days (13.3 vs 16.9 days with placebo; P=0.0006).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
blockers, coronary reperfusion therapy)				
Adamopoulos et al.[53] (2010) EPHESUS Eplerenone 25 mg daily for 4 weeks, followed by titration to 50 mg daily vs placebo once daily Patients were allowed to receive optimal medical therapy (ACE inhibitors, ARBs, diuretics, β-blockers, coronary reperfusion therapy)	DB, MC, RCT (post-hoc analysis based on the median time to initiation of treatment) Patients with acute myocardial infarction, left ventricular dysfunction (EF ≤40%), and heart failure (patients with diabetes were not required to have heart failure)	N=6,632 16 months	Primary: All-cause mortality, combined endpoint of cardiovascular (CV) hospitalization or CV death, and sudden cardiac death (SCD)	Primary: Patients assigned to 'earlier' eplerenone treatment (<7 days) had lower event rates compared to 'earlier' placebo administration for all cause mortality (11.5% vs 16.1%; P<0.0001), CV hospitalization/CV mortality (24% vs 30.3%; P<0.0001), and SCD (3.7% vs 6.9%; P<0.0001). There was no significant difference found between 'later' eplerenone patients (≥7 days) and placebo for all cause mortality (16.5% vs 17.1%; P=NS), CV hospitalization/CV mortality (28.5% vs 29.8%; PNS), or SCD (5.7% vs 5.5%; P=NS). After adjustment for other risk factors, earlier eplerenone initiation (<7 days) reduced the risk of all-cause mortality (HR 0.72; 95% CI, 0.58 to 0.89; P=0.002), CV hospitalization/CV mortality (HR 0.78, 95% CI: 0.67 to 0.90; P=0.001), and SCD (HR 0.54; 95% CI, 0.38–0.77; P=0.001). Later eplerenone initiation (≥7 days) was not associated with a reduction of risk for any of the endpoints.
Udelson et al.[64] (2010) Eplerenone 50 mg QD vs placebo	RCT, DB, PC, MC Patients ≥21 years of age with mild-to-moderate heart failure (NYHA class II to III) and LVEF ≤35% who were receiving standard heart failure therapy (ACE inhibitor or	N=226 36 weeks	Primary: Change in LV end-diastolic volume index (EDVi) Secondary: Changes in LV end-systolic volume index (LVESVi), LV	Primary: Over 36 weeks of treatment, there was no evidence of an effect of eplerenone on LVEDVi compared to placebo. Secondary: After 36 weeks, there was no evidence of an effect of eplerenone on LVESVi or LVEF compared with placebo. Systolic BP change was 0±16 mm Hg in the eplerenone group and was 0±16 mm Hg in the placebo group. Diastolic blood pressure change was -1±9 mm Hg in the eplerenone group and 0±11 mm Hg in the placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	ARB and β-blocker)		ejection fraction (LVEF), BP, and markers of collagen turnover	group. There was a greater reduction in procollagen type I N-terminal propeptide (PINP) and B-type natriuretic peptide (BNP) in the eplerenone group when compared with the placebo group (P=0.01 and P=0.04, respectively). There was no difference in procollagen type III N-terminal propeptide (PIIINP) between eplerenone and placebo. There were no differences in the inflammatory markers CRP and osteopontin during the course of therapy. Hyperkalemia was reported in 12% of patients during eplerenone therapy and in 6% of patients during placebo therapy.
Pitt et al.[32] (1999) RALES Spironolactone 25 to 50 mg QD vs placebo	DB, I, MC, RCT Patients with NYHA class III-IV, left ventricular EF ≤35%, and congestive heart failure for ≥6 weeks who were being treated with an ACE inhibitor and a loop diuretic	N=1,663 24 months (mean)	Primary: Death from any cause Secondary: Death from cardiac causes, hospitalization for cardiac causes, the combined incidence of death or hospitalization for cardiac causes, combined end point of death or hospitalizations from any cause, combined end point of death from any cause or hospitalizations from cardiac causes, change in the NYHA class,	Primary: There were 386 deaths from any cause with placebo and 284 deaths with spironolactone (RR, 0.70; 95% CI, 0.60 to 0.82; P<0.001). Secondary: There were 314 deaths in the placebo group and 226 deaths in the spironolactone group that were attributed to cardiac causes (RR, 0.69; 95% CI, 0.58 to 0.82; P<0.001). There were 753 hospitalizations for cardiac causes in the placebo group and 515 in the spironolactone group (RR, 0.70; 95% CI, 0.59 to 0.82; P<0.001). The combined end point of death from cardiac causes or hospitalizations from cardiac causes showed a 32% reduction in risk among patients in the spironolactone group as compared with those in the placebo group (RR, 0.68; 95% CI, 0.59 to 0.78; P<0.001). The combined end point of death or hospitalizations from any cause showed a 23% reduction in risk among patients in the spironolactone group as compared with those in the placebo group (RR, 0.77; 95% CI, 0.68 to 0.86; P<0.001). The combined end point of death from any cause or hospitalizations from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events	cardiac causes showed a 32% reduction in risk among patients in the spironolactone group as compared with those in the placebo group (RR, 0.68; 95% CI, 0.60 to 0.77; P<0.001). A significantly greater percentage of patients receiving spironolactone experienced improvement in the NYHA class compared to patients receiving placebo (41% vs 33%; P<0.001). Gynecomastia or breast pain was reported in 10% of men receiving spironolactone as compared to 1% of men in the placebo group (P<0.001). Incidence of hyperkalemia was minimal in both groups.
Chan et al.[33] (2007) Spironolactone 25 mg daily and candesartan 8 mg (combination group) vs candesartan 8 mg (control group)	DB, PC, RCT Patients with LVEF <40% on ACE inhibitors >6 months	N=48 1 year	Primary: Change in LVEF, left ventricular end-diastolic volume index, end-systolic volume index, left ventricular mass index, SBP, quality of life	Primary: At 1 year, combination therapy was associated with a significant improvement in LVEF from baseline (P<0.01). At 1 year, combination therapy was associated with a significant reduction in left ventricular end-diastolic volume index from baseline (P<0.001). At 1 year, combination therapy was associated with a significant reduction in end-systolic volume index from baseline (P<0.0005). At 1 year, combination therapy was associated with a significant reduction in left ventricular mass index from baseline (P=0.002). At 1 year, combination therapy was associated with a significant reduction in SBP from baseline (P<0.05). The control group was not associated with significant improvements in any of the above primary outcome measures. The quality of life score improved in both study groups.
Levy et al.[24] (1977) Spironolactone 25 mg daily, HCTZ 25 mg daily,	DB, RCT Patients 27 to 79 years of age with arteriosclerotic heart disease,	N=32 24 weeks	Primary: Change in heart failure symptoms, glucose, renin concentration, calcium, blood	Primary: The combination therapy group and furosemide monotherapy group exhibited comparable control of heart failure symptoms. The combination therapy group was associated with a significant decrease in glucose and an increase in plasma renin concentration compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination entity, for 16 weeks following 8 weeks of furosemide monotherapy vs furosemide 25 mg daily for 24 weeks	hypertensive heart disease, or rheumatic heart disease classes I-III, and congestive heart failure requiring diuretic therapy		urea nitrogen, uric acid, creatinine, aldosterone, serum potassium level, adverse effects	furosemide monotherapy group (P<0.01). There were no significant differences in calcium, blood urea nitrogen, uric acid, or creatinine between the study groups. There was a significant increase in aldosterone secretion among patients randomized to the spironolactone and HCTZ group compared to the furosemide group (P<0.01). There was no significant difference in serum potassium level between treatment groups. No serious adverse effects were observed in either of the study groups.
Hyperaldosteronism				
Karagiannis et al.[34] (2008) Eplerenone 25 mg twice daily, titrated up to 200 mg daily if blood pressure remained ≥140/90 mm Hg vs spironolactone 25 mg twice daily, titrated up to 400 mg daily if blood pressure remained ≥140/90 mm Hg HCTZ 12.5 mg was added to the study regimen if blood pressure remained	OL, PRO, R Patients with bilateral hyperaldosteronism	N=34 16 weeks	Primary: Percentage of patients whose blood pressure <140/90 mm Hg at week-16 Secondary: Adverse events	Primary: At 16 weeks, 76.5% and 82.4% of patients randomized to receive spironolactone and eplerenone therapies, respectively, exhibited reductions in blood pressure to <140/90 mm (P=10). Secondary: Serum potassium levels were normalized in all study groups at 4 weeks of therapy. Mild hyperkalemia was noted in two patients receiving spironolactone 400 mg and in three patients on eplerenone 150 mg therapy. Two patients receiving spironolactone reported bilateral gynecomastia at week-16. Switching from spironolactone 400 mg to eplerenone 150 mg daily was effective in resolving gynecomastia symptoms without disrupting blood pressure control.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
uncontrolled at week 16.				
Hypertension				
White et al.[40] (2003) Eplerenone 25 mg once daily vs eplerenone 50 mg once daily vs eplerenone 100 mg once daily vs eplerenone 200 mg twice daily vs placebo	DB, MC, RCT Adult patients, average age 53 years, with untreated hypertension and seated SBP <180 mm Hg, DBP between 95-110 mm Hg, and the 24-hour mean DBP ≥85 mm Hg	N=400 12 weeks	Primary: Mean change from baseline in seated DBP at 12 weeks Secondary: Change from baseline in SBP, 24-hour SBP and DBP, heart rate, adverse events	Primary: The eplerenone 50, 100, and 200 mg treatment groups experienced significant mean reductions in DBP from baseline compared to placebo (P≤0.01). The reduction in blood pressure in the eplerenone 25 mg group failed to meet statistical significance (P=0.10). Secondary: The eplerenone 50, 100, and 200 mg treatment groups experienced significant mean reductions in SBP from baseline compared to placebo (P≤0.01). All eplerenone treatment groups experienced statistically significant reductions in 24-hour ambulatory blood pressure measurements compared to placebo (P<0.006 for SBP and P<0.005 for DBP). There were no significant differences from baseline in 24-hour mean heart rate with any of the treatment groups compared to placebo. Treatment emergent adverse events were reported in 48% of the eplerenone-treated group and 49% of the placebo-treated group. None of the adverse events were statistically different between the groups. Two cases of impotence, gynecomastia, menstrual abnormalities and female breast pain were reported during the study; one case occurred in the placebo group and the other in the eplerenone 100 mg daily group.
Krum et al.[37] (2002) Eplerenone 50 to 100 mg daily vs placebo	DB, MC, PG, RCT Patients 18 and 85 years of age taking an ACE inhibitor or an ARB for mild-to-moderate hypertension (DBP ≥95 but <110 mm Hg and SBP <180	N=341 8 weeks	Primary: Mean change from baseline in trough cuff seated DBP and SBP at week-8 Secondary: The percentage of responders (defined as patients	Primary: Eplerenone-treated patients exhibited a statistically significant mean reduction from baseline in SBP compared with placebo at 8 weeks of therapy (P≤0.05), regardless of concurrent ACE inhibitor or ARB use. While eplerenone/ARB -treated patients exhibited a statistically significant mean reduction from baseline in DBP compared with placebo/angiotensin receptor blocker at 8 weeks of therapy (P≤0.05), patients receiving the eplerenone/ACE inhibitor combination therapy experienced a reduction in baseline DBP similar to placebo/ACE inhibitor therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study medications were added to background ACE inhibitor or ARB monotherapy.	mm Hg), with potassium >3.0 mEq/L but ≤5.0 mEq/L		who had a DBP<90 mm Hg or exhibited ≥10 mm Hg reduction from baseline), adverse events	Secondary: Significantly greater percentage of patients in the eplerenone/ARB groups exhibited a positive response to therapy compared to placebo/ARB-treated patients (P=0.003). No significant differences in response rate were observed between the eplerenone/ACE inhibitor and the placebo/ACE inhibitor groups. Adverse effects were mild-moderate and were similar in the eplerenone and placebo-treated groups.
Weinberger et al.[39] (2002) Eplerenone 50 mg once daily vs eplerenone 25 mg twice daily vs eplerenone 100 mg once daily vs eplerenone 50 mg twice daily vs eplerenone 400 mg once daily vs	DB, MC, PG, RCT Patients 21 to 80 years of age, with seated, cuff-assessed DBP ≥95 mm Hg but <114 mm Hg, a 24-hour mean DBP >85 mm Hg	N=409 8 weeks	Primary: Mean change in seated DBP from baseline Secondary: Mean change from baseline in SBP, 24-hour SBP and DBP, renin, aldosterone levels	Primary: Eplerenone therapy, across all doses studied, was associated with a statistically significant reduction from baseline in seated and standing DBP compared to placebo (P<0.05). Eplerenone 50 mg twice daily regimen was associated with a statistically significant reduction in baseline seated and standing DBP compared to eplerenone 100 mg once daily group (P<0.05). However, there were no differences in DBP reduction between any of the other once daily and twice daily eplerenone regimens. Compared with placebo, spironolactone was associated with statistically significant reductions in DBP (P≤0.001). Eplerenone 50 mg twice daily and 100 mg daily regimens were associated with DBP reduction approximately comparable to 50%-75% of effect observed with spironolactone 50 mg twice daily therapy. Secondary: Eplerenone therapy, across all doses studied, was associated with a statistically significant reduction from baseline in seated and standing SBP compared to placebo (P<0.05). Eplerenone 200 mg twice daily regimen was associated with a statistically significant reduction in baseline seated and standing SBP compared to eplerenone 400 mg once daily group (P<0.05). However, there were no differences in SBP reduction between any of the other once daily and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
eplerenone 200 mg twice daily vs spironolactone 50 mg twice daily vs placebo				twice daily eplerenone regimens. Eplerenone, across all doses studied, was associated with a statistically significant reductions in ambulatory SBP and DBP compared with placebo, as observed during a 24-hour monitoring (P<0.05). Compared with placebo, spironolactone was associated with statistically significant reductions in SBP (P≤0.001). Eplerenone 50 mg twice daily and 100 mg once daily regimens were associated with SBP reduction approximately comparable to 50% to 75% of effect observed with spironolactone 50 mg twice daily therapy. The incidence of adverse events in the eplerenone-treated patients was similar to placebo. Additionally, the incidence of adverse events was comparable in the eplerenone and spironolactone groups. Spironolactone 50 mg twice daily group was associated with a statistically significant increase from baseline in serum potassium level compared to the eplerenone 50 mg/day and 100 mg/day groups, regardless of once-daily or twice-daily dosing (P<0.05). Eplerenone therapy was not associated with an increased incidence of gynecomastia or impotence compared to placebo. There were no treatment-related menstrual abnormalities reported with eplerenone, while one patient in the spironolactone group reported treatment related intermenstrual bleeding.
Hollenberg et al.[36] (2003) Eplerenone 50 to 200 mg QD vs amlodipine 2.5 to 10 mg QD	RCT Patients ≥50 years of age with SBP between 140 to 190 mm Hg	N=269 24 weeks	Primary: Change in SBP and DBP, discontinuation rate, symptom distress index, SF-36 Health Survey	Primary: Both treatment groups exhibited similar reduction in SBP and DBP from baseline (P=0.01). The dropout rate was 50% greater in the amlodipine group compared to the eplerenone group. Symptom distress (technique used to assess the influence of drug treatment on quality of life) index was assessed and results favored eplerenone vs amlodipine (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				SF-36 Health Survey showed no significant difference between the two treatments. Both treatment groups experienced similar incidences of adverse effects. Eplerenone-treated patients did not develop breast pain/tenderness, breast enlargement, change in menstruation, gynecomastia, or loss of libido.
White et al.[41] (2003) Eplerenone 50 to 200 mg QD vs amlodipine 2.5 to 10 mg QD	AC, DB, MC, R Patients ≥50 years of age with systolic hypertension (seated clinic SBP 150 to 165 mm Hg with a pulse pressure ≥70 mm Hg or 165 to 200 mm Hg with a DBP ≤95 mm Hg)	N=269 24 weeks	Primary: Mean change from baseline in SBP, DBP, 24-hour ambulatory blood pressure, pulse pressure, and heart rate at week-24, albumin/creatinine ratio, adverse events	Primary: Mean reduction in SBP from baseline was comparable in the eplerenone and amlodipine groups (P=0.83). Eplerenone was associated with statistically significant reductions in DBP from baseline at 24 weeks of therapy compared to amlodipine (P=0.014). The two treatment groups exhibited comparable decreases in 24-hour ambulatory blood pressure, pulse pressure, and heart rate after 24 weeks of therapy (P>0.05). Eplerenone was associated with a statistically significant reduction from baseline in the albumin/creatinine ratio compared to amlodipine (P=0.002). Treatment-emergent adverse events were reported in 64% of the eplerenone group and 70% of the amlodipine group. The only adverse event that was significant between the groups was the incidence of edema (25.5% for amlodipine vs 3.7% for eplerenone; P<0.05). There were no reports of gynecomastia, breast tenderness, or menstrual irregularities in either group.
Williams et al.[42] (2004) Eplerenone 50 to 200 mg QD vs enalapril 10 to 40	AC, DB, MC, PG, R Patients ≥18 years of age with stage 1 to 2 hypertension (seated DBP ≥90 but <110 mm Hg, with a seated SBP <190 mm Hg)	N=499 12 months	Primary: Change in seated trough DBP at month-6 Secondary: Change in seated trough SBP at month-6, reduction	Primary: At 6 months of therapy both treatment groups exhibited comparable reductions in DBP from baseline (P=0.91). Secondary: At 6 months of therapy both treatment groups exhibited comparable reductions in SBP from baseline (P=0.20). At 12 months of therapy both treatment groups exhibited comparable

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD			in SBP and DBP at month-12, reduction in UACR, adverse events	reductions in SBP and DBP from baseline (P=0.25, P=0.33). Eplerenone was associated with a statistically significant reduction from baseline in UACR compared to enalapril (61.5% vs 25.7%; P=0.01). There were no significant differences in overall treatment-emergent adverse events between the two treatment groups. There were no sex hormone related adverse events in the eplerenone group. There were no clinically significant differences in the groups in any of the laboratory tests assessed. There were two patients in the eplerenone and two patients in the enalapril group that experienced hyperkalemia of ≥5.5 mmol/L.
Flack et al.[35] (2003) Eplerenone 50 mg daily vs losartan 50 mg daily vs placebo	DB, MC, PG, RCT Patients ≥18 years of age with mild-to-moderate hypertension, with SBP <180 mm Hg and DBP 95 to 109 mm Hg (off medication) or if patients were receiving antihypertensive therapy their blood pressure was <140/90 mm Hg	N=551 16 weeks	Primary: Mean change from baseline in DBP at 16 weeks Secondary: Mean change from baseline at 16 weeks in SBP, SBP and DBP within and between racial groups, response rate (defined as the percentage of patients with DBP <90 mm Hg or DBP ≥90 mm Hg but ≥10 mm Hg below baseline), urinary albumin/creatinine ratio, effect of eplerenone in patients with various baseline renin and	Primary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in DBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). Secondary: At 16 weeks, patients randomized to eplerenone exhibited significantly greater mean changes in SBP from baseline compared to either losartan- or placebo-treated groups (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated African American patients (P<0.001). At 16 weeks, African American patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the losartan-treated African American patients (P≤0.001). At 16 weeks, white patients randomized to eplerenone exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated white patients (P=0.001). However, the difference in SBP- and DBP-lowering effects was not significant different between the eplerenone ad losartan groups (P=0.126, P=0.068, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			aldosterone levels, adverse effects	Significantly greater percentage of patients randomized to eplerenone exhibited a positive response to therapy compared to either placebo (64.5% vs 41.2%; P<0.001) or losartan group (64.5% vs 48.3%; P=0.003). The eplerenone group (regardless of race) exhibited statistically significant improvement in urinary albumin/creatinine ratio from baseline compared to placebo (P=0.003). However, the difference in urinary albumin/creatinine ratio change from baseline was not significantly different between the eplerenone and losartan groups (P=0.652). Compared to losartan, eplerenone was more effective in lowering SBP and DBP in patients with low-moderate baseline renin levels (P<0.05). However, the difference was not statistically significant in patients with high baseline renin levels. Compared to losartan, eplerenone was more effective in lowering SBP in patients with low or high baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate baseline aldosterone levels. Compared to losartan, eplerenone was more effective in lowering DBP in patients with low baseline aldosterone levels (P<0.05). However, the difference was not statistically significant in patients with moderate-high baseline aldosterone levels. There were no significant differences in the incidence of adverse events noted in eplerenone, placebo or losartan groups. The reported incidence of gynecomastia, breast pain, menstrual abnormalities, impotence, hyperkalemia and decreased libido with eplerenone was low and comparable to losartan and placebo.
Schersten et al.[38] (2002) Spironolactone 50 mg daily	RCT, SB, XO Patients <75 years of age, with DBP between 105 to 135 mm Hg, after 10 to	N=45 11 months	Primary: Change from baseline in DBP and SBP, adverse effects	Primary: Each of the three spironolactone groups were associated with significantly reduced blood pressure levels from baseline as compared to placebo (P<0.001). While spironolactone 200 mg daily lowered mean supine SBP more than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs spironolactone 100 mg daily vs spironolactone 200 mg daily vs placebo	15 minutes of supine rest			the spironolactone 50 mg daily therapy (P<0.05), the difference between spironolactone 50 mg and 100 mg/day was not statistically significant. Spironolactone 200 mg daily was associated with a significant reduction in mean upright SBP from baseline compared with either of the lower dose groups (P<0.01). The difference in the lowering of DBP from baseline was not statistically different among any of the three active treatment groups. Spironolactone 100 mg/day therapy was associated with a statistically significant increase in baseline potassium and serum creatinine concentrations (P<0.05). However, spironolactone 50 mg was not associated with a change in potassium level from baseline.
Li et al.[59] (2010) <u>Phase A</u> Spironolactone 25 mg QD (low-dose), 25 mg BID (middle-dose), 50 mg BID (high-dose) for 6 weeks <u>Phase B</u> Spironolactone 25 mg QD, 25 mg BID, 50 mg BID for 4 weeks vs placebo	RCT, MC, DB, PC Children 4-16 years of age with systolic blood pressure (SBP) ≥95th percentile	N=304	Primary: Change in systolic BP (SBP) during phase B Secondary: Change in diastolic BP and safety	Primary: Change in SBP from baseline of phase B to the end of the study (differences from placebo) were -2.61, +2.32, and -2.76 mm Hg for the low-, middle-, and high-dose groups, respectively (P=NS, P=NS, P=0.048, respectively). Secondary: There were no significant effects of eplerenone on change in DBP from baseline of phase B to end of study compared to placebo. During phase A, adverse events were reported by 40.2% of subjects in the high-dose group, 30.6% of those in the middle-dose group, and 37.9% of those in the low-dose group. In phase B, there were no differences in adverse event frequencies between active therapy and placebo (high-dose: 38.4% vs 45.2%; middle-dose: 50.0% vs 25.0%; low-dose 26.9% vs 34.6%, eplerenone vs, placebo, respectively). Serious adverse events in phase A included diarrhea, sleep apnea, syncope, pericarditis, arthritis, pneumonia, sepsis, and pleural effusion. In phase B, serious adverse events included sleep apnea, abdominal pain, and fever.
Hood et al.[45] (2007)	DB, RCT, XO Patients with seated	N=57 42 weeks	Primary: Change in blood pressure and	Primary: Spironolactone 100 mg and bendroflumethiazide 5 mg daily regimens were not associated with a statistically significant difference in blood

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SALT Spironolactone 50 mg daily vs spironolactone 100 mg daily vs amiloride 20 mg daily vs amiloride 40 mg daily vs bendro-flumethiazide 2.5 mg daily vs bendro-flumethiazide 5 mg daily vs losartan 100 mg daily	blood pressure of 140/90 to 170/110 mm Hg, plasma renin of 12 mU/L, plasma aldosterone-renin ratio >750, previous fall in SBP ≥20 mm Hg after 1 month of open-label treatment with spironolactone 50 mg daily		plasma renin from baseline between spironolactone 100 mg and bendro-flumethiazide 5 mg daily regimens Secondary: Change in blood pressure and plasma renin from baseline between amiloride and other diuretics and between lower and higher doses of each diuretic	pressure reduction from baseline. Secondary: Spironolactone 50 mg was associated with a statistically significant decrease in blood pressure from baseline compared with bendroflumethiazide 2.5 mg daily therapy (P<0.01). Losartan 100 mg was associated with a statistically significant decrease in blood pressure from baseline compared with bendroflumethiazide 2.5 mg daily therapy (P<0.05). High-dose bendroflumethiazide and amiloride regimens were associated with statistically greater reductions in blood pressure compared to the lower doses (P<0.05). Spironolactone was associated with a four-fold increase in baseline renin level compared to a two-fold increase observed with bendroflumethiazide therapy (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo daily				
Nash et al.[25] (1977) Spironolactone 50 mg twice daily vs spironolactone 100 mg twice daily vs spironolactone 200 mg twice daily vs HCTZ 50 mg twice daily vs spironolactone 25 mg and HCTZ 25 mg twice daily (fixed-dose combination)	DB, RCT Male outpatients between the ages of 21 to 65 years, with essential hypertension, DBP between 90 to 114 mm Hg; patients were excluded if they had DBP >114 mm Hg, severe renal, hepatic, endocrine, gastrointestinal disease, recent myocardial infarction, congestive heart failure, or severe angina	N=79 12 weeks	Primary: Change in SBP, DBP, blood urea nitrogen, serum potassium, gynecomastia	Primary: At week-12, all study groups exhibited significant reductions in SBP and DBP from baseline (P<0.05). At week-12, all 3 spironolactone monotherapy groups exhibited statistically significant increases in blood urea nitrogen from baseline (P<0.05). At week-12, the HCTZ monotherapy group was associated with a statistically significant decrease in serum potassium levels (P<0.001). At week-12, all 3 spironolactone monotherapy groups exhibited statistically significant increases in serum potassium levels from baseline (P<0.05). At week-12, the spironolactone-hydrochlorothiazide combination group was not associated with statistically significant increases in serum potassium levels from baseline. A dose-related risk of gynecomastia was observed in the spironolactone-treated patients. Among patients treated with spironolactone 50, 100, or 200 mg twice daily, 5.5%, 11.8%, and 40% reported gynecomastia symptoms. Of the patients randomized to spironolactone/hydrochlorothiazide combination product, 7.7% reported gynecomastia symptoms.
Schrijver et al.[26] (1979) Spironolactone 50 mg twice daily for 8 weeks (single drug	C, DB Patients, between 24 to 63 years of age, with DBP between 90 to 114 mm Hg;	N=49 20 weeks (4-week placebo run-in, 8-week single	Primary: Change in MABP, serum potassium, uric acid level, blood glucose, blood urea	Primary: Following 8 weeks of therapy with a single drug, all study groups exhibited a statistically significant reduction in MABP from baseline (P<0.01). There were no significant differences in MABP reduction among the study groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
phase), with the addition of a placebo for subsequent 4 weeks (group IA) vs spironolactone 50 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ 50 mg twice daily was added to the regimen for an additional 4 weeks (group IB) vs spironolactone 100 mg twice daily for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIA) vs spironolactone 100 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ	patients were excluded if they had secondary hypertension, congestive heart failure, angina, blood urea nitrogen >25 mg%	drug therapy, 4-week two-drug therapy, 4-week recovery)	nitrogen, creatinine, plasma renin activity, aldosterone, side effects	The addition of a second drug to the antihypertensive regimen was not associated with a significant improvement in MABP. At the end of the two-drug treatment period, there were no differences in MABP among any of the study groups. Spironolactone therapy was associated with a significant decrease in serum potassium concentration from baseline (P<0.001). Spironolactone regimens were not associated with a significant change in potassium levels from baseline. Following 8 weeks of therapy with a single drug, HCTZ-treated patients experienced a statistically significant increase in uric acid from baseline (P<0.001). Groups IIA and IIB also experienced a significant but smaller increase in uric acid level from baseline (P<0.05) with no change in groups I and IV. During the single-drug treatment phase, patients randomized to group I experienced a significant increase in blood glucose from baseline (P<0.05). During the single-drug treatment phase, all patients except those randomized to group I experienced a significant increase in blood urea nitrogen from baseline (P<0.05). During the single-drug treatment phase, patients randomized to groups I and II experienced a significant increase in serum creatinine from baseline (P<0.05). During the single-drug treatment phase, all treatment groups experienced a significant increase in plasma renin activity from baseline (P<0.01). The addition of HCTZ in the two-drug study phase was associated with a rise in plasma renin activity in all study groups (P<0.05). All treatment groups experienced a significant increase in plasma aldosterone from baseline (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 mg twice daily was added to the regimen for an additional 4 weeks (group IIB) vs spironolactone 200 mg twice daily for 8 weeks (single drug phase), with the addition of a placebo for subsequent 4 weeks (group IIIA) vs spironolactone 200 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ 50 mg twice daily was added to the regimen for an additional 4 weeks (group IIIB) vs hydrochlorothiazide 50 mg twice daily for 8 weeks (single drug phase), with the addition of a				Gynecomastia was reported only by patients randomized to the higher-dose spironolactone groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo for subsequent 4 weeks (group IVA) vs hydrochlorothiazide 50 mg twice daily for 8 weeks (single drug phase), subsequently HCTZ 50 mg twice daily was added to the regimen for an additional 4 weeks (group IVB)				
Wray et al.[62] (2010) Spironolactone 25 to 100 mg QD vs HCTZ 12.5 to 50 mg QD Patients also received potassium 0-40 mEq to maintain blinding.	RCT, DB Patients ≥60 years of age with stage 1 hypertension	N=36 6 months	Primary: Blood pressure and sympathetic nervous system (SNS) activity	Primary: Arterial blood pressure decreased significantly with spironolactone (SBP: 160 to 134 mm Hg and DBP: 77 to 68 mm Hg) and with hydrochlorothiazide (SBP: 161 to 145 mm Hg and 78 to 73 mm Hg). There was no significant difference between the groups. Sympathetic nervous system activity was significantly reduced after spironolactone (plasma NE: 378 to 335 pg/mL; P=0.04; [^{3}H]-NE release rate: 2.74 to 1.97 mcg/min/m^2; P=0.04), but not with hydrochlorothiazide (plasma NE: 368 to 349 pg/mL; P=0.47; [^{3}H]-NE release rate: 2.63 to 2.11 mcg/min/m^2; P=0.21). There were no instances of hyperkalemia, and no other adverse effects were reported.
Bomback et al.[55] (2009) Spironolactone 12.5 mg QD for 4 weeks in addition to ACE	OL Patients with obesity, longstanding hypertension and	N=21 8 weeks	Primary: Change in 24-hour ambulatory BP, changes in office BP, nocturnal BP and	Primary: Mean office, 24-hour ambulatory, and nocturnal ambulatory blood pressures declined significantly during the 4 weeks of spironolactone therapy from 110.6 to 105.0 mm Hg (office P=0.004), 100.6 to 95.5 mm Hg (24-hour P=0.03) and 95.3 to 87.5 mm Hg (nocturnal P=0.004).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitor therapy	evidence of target organ damage who were treated with ACE inhibitors		urine albumin : creatinine ratio (UACR)	The mean UACR dropped from 13.8 to 8.5 mg/g (P=0.002) during spironolactone therapy and returned to 13.2 mg/g after the drug was withdrawn. Serum potassium was not significantly affected by spironolactone therapy. There was a significant increase in serum creatinine from 0.95 before therapy to 1.03 mg/dl after spironolactone. The eGFR decreased from 81.9 to 76.8 ml/min/1.73m^2.
Chapman et al.[43] (2007) ASCOT-BPLA Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendro-flumethiazide/K 1.25 to 2.5 mg and doxazosin were added for additional blood pressure control; if blood pressure remained elevated on three above drugs, spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target	RCT (post-hoc analysis) Men and women, aged 40 to 79 years with hypertension and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)	N=1,411 1.3 years	Primary: Change in DBP and SBP, adverse effects	Primary: Spironolactone treatment lead to a significant 21.9 mm Hg reduction in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm Hg; P<0.001). Spironolactone treatment lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1 mm Hg; P<0.001). Spironolactone therapy was associated with small but significant decreases in sodium, low-density lipoprotein and total cholesterol as well as increases in potassium, glucose, creatinine, and high-density lipoprotein cholesterol (P<0.05). The most common adverse effect reported in the study was gynecomastia in men.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and doxazosin were added for additional blood pressure control; if blood pressure remained elevated on three above drugs, spironolactone 25 mg was added to the regimen				
Diabetes/Diabetic Nephropathy/Renal Disease				
Bianchi et al.[47] (2006) Spironolactone 25 mg daily in addition to conventional therapy (ACE inhibitor and/or ARB) vs conventional therapy (ACE inhibitor and/or ARB)	OL, PRO, R Patients, aged 54.7 years on average, with idiopathic chronic glomerulonephritis and proteinuria >1 g/g creatinine	N=165 1 year	Primary: Change in proteinuria, eGFR, blood pressure, and serum potassium	Primary: While there was a significant reduction in proteinuria from baseline among patients treated with spironolactone (P<0.001), there was no difference in the conventional therapy group (P>0.05). At one year, there was no significant difference between groups in eGFR. However, spironolactone treatment was associated with a lower monthly rate of decrease in eGFR from baseline compared conventional therapy (P<0.01). Patients whose baseline eGFR was <60 mL/min experienced a greater decline in eGFR compared to patients with baseline eGFR >60 mL/min (P<0.01). At one year of therapy, patients receiving spironolactone in addition to conventional therapy experienced a reduction in blood pressure from baseline (P<0.05). In contrast, those randomized to the conventional therapy group did not exhibit blood pressure reduction from baseline. While there was a significant increase in serum potassium from baseline among patients treated with spironolactone (P<0.001), there was no difference in the conventional therapy group (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bianchi et al.[54] (2010) Spironolactone 25 mg, ramipril 10 mg, irbesartan 300 mg, and atorvastatin 10 mg QD (intensive therapy) vs ramipril 10 mg and atorvastatin 10 mg QD (conventional therapy) The addition of diuretics, calcium antagonists, β-blockers or α1-receptor antagonists were added to achieve BP <130/80 mm Hg	RCT, OL Patients with a clinical diagnosis of idiopathic chronic glomerulonephritis (GN) and urine protein-creatinine ratio >1 g/g	N=128 36 months	Primary: Changes over time in proteinuria and eGFR Secondary: Adverse events and drop outs	Primary: Systolic BP decreased more in the intensive-therapy group (from 156.6 to 113.5 mm Hg) than in the conventional therapy group (from 155.7 to 122.7 mm Hg; P<0.01). Urine protein excretion decreased from 2.65 to 0.45 g/g creatinine with intensive therapy (P<0.001). With conventional therapy, urine protein excretion decreased from 2.60 to 1.23 g/g creatinine (P<0.001). With intensive therapy, eGFR did not significantly change over time (64.6 vs 62.9 mL/min/1.73 m^2). With conventional therapy, eGFR decreased from 62.5 to 55.8 mL/min/1.73 m^2 (P<0.01). Secondary: In the conventional therapy group, 8 patients discontinued the study due to hyperkalemia, cough, and rapid deterioration in kidney function. In the intensive therapy group, 15 dropped out due to hyperkalemia, cough, and hypotension. Nine patients in the intensive therapy group developed gynecomastia. Twelve patients on conventional and 31 on intensive therapy had to interrupt the study temporarily because of low BP. No patient developed an increase in creatine kinase, alanine aminotransferase, and alkaline phosphatase levels during the study.
Ogawa et al.[44] (2006) Spironolactone 25 mg daily in addition to imidapril* 5 mg daily vs furosemide 20 mg	RCT Patients, 62.3 years of age on average, with hypertension and type II diabetes, with a urinary albumin/creatinine ratio >30 mg/g creatinine, and plasma B-type	N=30 24 months	Primary: Change in B-type natriuretic peptide, albumin/creatinine ratio, blood pressure	Primary: At 12 months, spironolactone therapy was associated with a significant reduction in B-type natriuretic peptide level from baseline compared with spironolactone therapy (P<0.05). At 12 months, spironolactone therapy was associated with a significant reduction in albumin/creatinine ratio from baseline compared with spironolactone therapy (P<0.05). Both study groups exhibited similar reductions in blood pressure from baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily in addition to imidapril* 5 mg daily	natriuretic peptide levels >100 pg/mL (suggestive of mild heart failure). All patients were pre-treated with imidapril* for one year prior to study onset.			No adverse events were reported in the study.
Chrysostomou et al.[48] (2006) Spironolactone 25 mg daily, in addition to irbesartan 150 mg daily and ramipril 5 mg daily vs ramipril 5 mg daily, in addition to spironolactone 25 mg daily and irbesartan placebo vs ramipril 5 mg daily, in addition to spironolactone placebo and irbesartan 150 mg daily	DB, PC, RCT Patients 18 to 75 years of age, with a 24-hour urinary protein excretion >1.5 g/24-hours on ≥2 occasions ≥3 months apart, serum creatinine level ≤200 µmol/L with <20% variability in the preceding 3 months, and treatment with an ACE inhibitor ≥6 months	N=41 6 months	Primary: Change in 24-hour urinary protein excretion at 3 months Secondary: Change in 24-hour urinary protein excretion at 6 months, change in blood pressure and creatinine clearance, adverse effects	Primary: Compared with the ramipril monotherapy group, the 24-hour urinary protein excretion reduction at 3-months was significantly greater in the ramipril and spironolactone groups (P=0.004). The ramipril, irbesartan, and spironolactone groups were associated with a significant reduction in 24-hour urinary protein excretion compared to the ramipril monotherapy group (P<0.001). There was no significant difference in 24-hour urinary protein excretion with the ramipril monotherapy group and the ramipril/irbesartan group (P=10). At three months of therapy, patients receiving spironolactone were associated with a significant reduction in proteinuria from baseline (P≤0.001). In contrast, those patients who were not receiving spironolactone did not experience a significant reduction in proteinuria from baseline (P=0.840). Secondary: At 6 months, patients receiving spironolactone therapy were associated with the greatest reduction in proteinuria compared to the other regimens (P<0.05). At 6 months, DBP was higher among patients randomized to the ramipril monotherapy group compared to other study regimens (P=0.046). There was no difference in SBP among the study groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ramipril 5 mg daily, in addition to spironolactone and irbesartan placebos				There were no differences in creatinine clearance among the study groups (P>0.05). Gynecomastia was not observed in any of the treatment groups.
Furumatsu et al.[49] (2008) Spironolactone 25 mg daily added to ongoing therapy consisting of enalapril 5 mg daily and losartan 50 mg daily (triple blockade group) vs trichlormethiazide 1 mg or furosemide 10 mg daily added to ongoing therapy consisting of enalapril 5 mg daily and losartan 50 mg daily (control group)	MC, OL, PRO, RCT Patients 20 to 70 years of age, with controlled blood pressure <130/80 mm Hg, chronic nephropathy (defined by serum creatinine level <3 mg/dL or calculated creatinine concentration <30 mL/min), daily treatment with enalapril 5 mg and losartan 50 mg for at least 12 weeks, and persistent proteinuria (urinary protein excretion >0.5 g/day)	N=32 12 months	Primary: Reduction in proteinuria, urinary type IV collagen, SBP, DBP, mean blood pressure, creatinine, creatinine clearance, potassium, urinary aldosterone	Primary: At one year of therapy, patients randomized to the triple blockage group experienced a statistically significant 58% reduction in urinary protein level from baseline (P<0.05), while there was no difference in the control group. Compared to the control group, the triple blockade group experienced a significant reduction in proteinuria at one year of therapy (P<0.05). At one year of therapy, patients randomized to the triple blockage group experienced a statistically significant 40% reduction in urinary type IV collagen from baseline (P<0.05); while there was no difference in the control group. However there was no statistically significant difference in the change of urinary type IV collagen from baseline between the two study groups. There were no statistically significant differences between the two study groups in the following outcome measures: SBP, DBP, mean blood pressure, creatinine, creatinine clearance, potassium, urinary aldosterone.
van den Meiracker et al.[50] (2006) Spironolactone 25 mg twice daily, in	DB, PC, PG, RCT Patients with type 2 diabetes, macroalbuminuria (24-hour urinary	N=59 1 year	Primary: Change in albuminuria, DBP and SBP, GFR, aldosterone level, plasma renin	Primary: Compared to placebo, spironolactone therapy was associated with a significant 40.6% reduction in albuminuria from baseline (P=0.002). Compared to placebo, spironolactone therapy was associated with a significant reduction in systolic blood pressure from baseline (P=0.04),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
addition to ongoing antihypertensive therapy vs placebo in addition to ongoing antihypertensive therapy	albumin excretion >300 mg or urinary albumin to creatinine ratio >20 mg/mmol) despite use of an ACE inhibitor or ARB in recommended dosages for at least 1 year		activity, and serum potassium	with comparable reduction in DBP. Both groups exhibited comparable changes in GFR from baseline. Compared to placebo, spironolactone therapy was associated with significant increases in aldosterone level and plasma renin activity from baseline (P<0.05). There was a significant increase in serum potassium level with spironolactone therapy compared to placebo (P=0.02).
Schjoedt et al.[51] (2006) Spironolactone 25 mg daily, in addition to ongoing antihypertensive therapy (ACE inhibitor or ARB) vs placebo in addition to ongoing antihypertensive therapy (ACE inhibitor or ARB)	DB, RCT, XO Patients with diabetic nephropathy and nephrotic range albuminuria (>2,500 mg/24 hour) despite recommended antihypertensive treatment	N=20 2 weeks	Primary: Change in proteinuria, ambulatory DBP and SBP, GFR, fractional albumin clearance, aldosterone level, plasma renin activity, and serum potassium	Primary: Compared to placebo, spironolactone therapy was associated with a significant 32% reduction in proteinuria from baseline (P<0.001). Compared to placebo, spironolactone therapy was associated with a significant reduction in systolic and diastolic ambulatory 24-hour blood pressures from baseline (P=0.004, P=0.001, respectively). Both groups exhibited comparable changes in GFR from baseline (P=0.13). Compared to placebo, spironolactone therapy was associated with a significant 31% reduction in fractional albumin clearance from baseline (P<0.001). Compared to placebo, spironolactone therapy was associated with significant increases in aldosterone level and plasma renin activity from baseline, 80% and 91%, respectively (P<0.005). There was a trend towards an increase in the serum potassium level with spironolactone therapy compared to placebo (P=0.054).
Davidson et al.[56] (2008) Spironolactone 25 mg added to existing ACE	OL Patients ≥18 years of age with type 2 diabetes on an ACE inhibitor for >1	N=24 12 weeks	Primary: Change in urinary albumin excretion (UAE) Secondary:	Primary: UAE decreased 25.7% from a 404.6 mg/d to 302.7 mg/d (P<0.001). UAE decreased 27.2% in the microalbuminuria group (P=0.05) and 24.3% in the macroalbuminuria group (P=0.02). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhibitor therapy	month with a urinary albumin to creatinine ratio >100 mg/g		Changes in serum creatinine, serum potassium, and systolic blood pressure	There were no significant changes in serum sodium, potassium, creatinine, or glucose. There was a significant decrease in systolic blood pressure with the addition of spironolactone (141.2 to 132.5 mm Hg; P=0.002).
Saklayen et al.[60] (2008) Spironolactone 25 to 50 mg added to existing ACE inhibitor or ARB therapy for 3 months vs placebo added to existing ACE inhibitor or ARB therapy for 3 months	R, DB, PC, XO Patients with diabetic nephropathy with any level of proteinuria who were already being treated with ACEI (lisinopril) or ARB (losartan) at moderate-to-maximum dose	N=30 7 months	Primary: Blood pressure (BP), serum creatinine, and spot urine protein/creatinine	Primary: With spironolactone, the mean systolic BP at the beginning of the treatment period was 153.64 mm Hg and 141.60 at the end (P=0.01). Diastolic BP was 79.56 mm Hg at baseline and 76.68 at study endpoint (P=0.25). The mean systolic BP with placebo was 154.52 mm Hg at the beginning of the treatment period and 148.82 mm Hg at the end of the study period (P=0.34). Diastolic BP was 79.74 mm Hg at baseline and 77.91 at study endpoint (P=0.49). The urine protein/creatinine increased from 1.24 to 1.57 (24%) with placebo (P=0.35) and decreased from 1.80 to 0.79 (57%) with spironolactone (P=0.004). Serum creatinine increased from 1.43 to 1.50 on placebo (P=0.19) and from 1.35 to 1.56 on spironolactone (P=0.006).
Sengul et al.[61] (2009) Spironolactone 25 mg QD added to existing ACE inhibitor or ARB therapy	PRO Patients with overt proteinuria (> 300 mg/day) despite the regular use of ACE inhibitors and/or ARBs for at least six months	N=33 8 weeks	Primary: Proteinuria and blood pressure	Primary: At week 4, there was a 25.4% reduction in proteinuria with spironolactone (P=0.003). Systolic and diastolic BP were significantly reduced (P=0.013 and P=0.040, respectively). Serum potassium level increased 0.28 mEq/L (P<0.001). At week 8, the 24-hour median urinary protein excretion decreased from 1428 mg/d to 743 mg/d (47.9%) with spironolactone. Systolic and diastolic BP were significantly reduced (P<0.004 and P<0.001, respectively. Serum potassium level increased 0.55 mEq/L (P<0.001). There was no difference in creatinine clearance or serum creatinine levels. Serum albumin increased from 3.88 to 4.01 g/dL (P=0.003).
Tylicki et al.[63] (2008)	R, OL, XO Patients with chronic	N=18 16 weeks	Primary: 24-hour urine excretion of	Primary: A total of 17 patients achieved BP goal of <130/80 mm Hg. There was no difference in ambulatory systolic and diastolic BP between the treatments

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Spironolactone 25 mg QD plus background therapy for 8 weeks (triple RAAS blockade) vs background therapy for 8 weeks (double RAAS blockade) Background therapy included HCTZ, telmisartan, cilazapril (ACE inhibitor).	nondiabetic proteinuric kidney diseases		protein (UPE), BP, serum creatinine, serum potassium, plasma renin activity	(P=0.9 and P=0.1). Serum creatinine and eGFR remained stable during the study periods (P=0.6 and P=0.9, respectively). A significant increase in plasma renin activity was observed after treatment with triple RAAS blockade compared with double RAAS blockade (P=0.02). Triple RAAS therapy provided an additional 55.37% decrease in proteinuria compared with double RAAS blockade (P=0.01). The decrease in proteinuria was shown in 16 of 18 patients. Changes in proteinuria did not correlate with changes in systolic BP, diastolic BP, or PRA. There was a significant increase in potassium levels after triple RAAS blockade compared with baseline (P=0.02).
Miscellaneous				
Pitt et al.[27] (2003) Eplerenone 200 mg tablet in addition to placebo capsule once daily vs enalapril 40 mg capsule in addition to placebo tablet once daily vs eplerenone 200 mg tablet in addition to	AC, DB, PG, RCT Patients with left ventricular hypertrophy, a history of hypertension and predominantly in sinus rhythm	N=153 9 months	Primary: Change in left ventricular mass as assessed by MRI Secondary: Reduction in SBP, DBP, response rate (DBP <90 mm Hg), change in UACR	Primary: Both treatment groups were associated with a significant reduction in left ventricular mass from baseline (P<0.001). The difference in left ventricular mass reduction from baseline between the two treatment groups was not statistically significant (P=0.258). While eplerenone/enalapril combination therapy group demonstrated significantly greater reduction in left ventricular mass from baseline compared to eplerenone monotherapy group (P=0.007), the effect was not statistically different from that observed in the enalapril monotherapy group (P=0.107). Secondary: The SBP was reduced significantly more with the eplerenone/enalapril combination group than with eplerenone alone (P=0.048). The other treatment groups exhibited statistically comparable reductions from baseline in mean SBP and DBP.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril 10 mg capsule once daily If the blood pressure was uncontrolled on study medication at week-8, open label HCTZ 12.5 to 25 mg daily and/or amlodipine 10 mg daily were allowed.				While 70.0% of eplerenone-treated patients responded to therapy, the response rate in the enalapril monotherapy group was only 40.7% (P=0.003). In addition, while 79.6% of eplerenone/enalapril-treated patients responded to therapy, the response rate in the enalapril monotherapy group was only 40.7% (P=0.001). Combination therapy was associated with a significant reduction in UACR compared to either eplerenone or enalapril monotherapy groups (P<0.05). Adverse events were reported with similar incidence among all treatment groups. Cough was significant in enalapril patients vs eplerenone patients (P=0.033). Two cases of gynecomastia were reported (one with eplerenone and one with eplerenone and enalapril). Four patients (three on enalapril and one on eplerenone and enalapril) experienced impotence during the study. Seven eplerenone, two enalapril, and three eplerenone/enalapril patients experienced serious hyperkalemia (≥6.0 mmol/L).
Taniguchi et al.[46] (2006) Spironolactone 25 mg QD and candesartan 8 mg QD for six months, following 6 months of therapy with candesartan monotherapy (combination group) vs candesartan 8 mg QD for 12 months	DB, RCT, XO Patients, 67 years of age on average, with essential hypertension and left ventricular hypertrophy	N=97 1 year	Primary: Change in blood pressure and relative wall thickness	Primary: Both study groups experienced a statistically significant reduction in blood pressure from baseline (P<0.05). While candesartan was associated with a significant reduction in relative wall thickness among patients with concentric left ventricular remodeling or hypertrophy (P<0.05), the addition of spironolactone did not provide additional benefit.
Edwards et al.[57] (2009)	RCT, DB, PC	N=115	Primary: Change in LV	Primary: Treatment with spironolactone resulted in significant reductions in LV

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Spironolactone 25 mg QD added to existing ACE inhibitor or ARB therapy vs placebo added to existing ACE inhibitor or ARB therapy	Patients 18-80 years of age with stage 2 and 3 chronic kidney disease (CKD) with controlled blood pressure (mean daytime ambulatory blood pressure <130/85 mm Hg) on and ACE inhibitors or ARB for 6 months	36 weeks	mass and arterial stiffness measured Secondary: Aortic distensibility, Aug AIx, blood pressure, and albuminuria	mass and LV mass index. The prevalence of LVH decreased by 50% with spironolactone ,but was unchanged with placebo. Spironolactone did not affect LV volumes or ejection fraction. Secondary: Treatment with spironolactone resulted in a significant decrease in pulse wave velocity, central aortic pressure augmentation, Aug Ix, and Aug Ix 75. Aortic distensibility increased with the use of spironolactone compared with placebo. Treatment with spironolactone resulted in a significant decrease in office systolic blood pressure (-11 vs -5 mm Hg, P<0.05), office pulse pressure (-5 mm Hg vs -1 mm Hg, P<0.05), central systolic blood pressure (-12 mm Hg vs -4 mm Hg, P<0.01), central mean arterial pressure (-8 mm Hg vs -4 mm Hg, P<0.05), and central pulse pressure (-5 mm Hg vs -1 mm Hg, P<0.01). Office, central, and ambulatory diastolic pressures were not different between treatment groups. Treatment with spironolactone was not associated with a significant decrease in eGFR compared to placebo (-3 ml/min/1.73 m^2 vs -1 ml/min/1.73 m^2, respectively; P=NS). Treatment with spironolactone reduced albuminuria by -21 mg/mmol compared with -8 mg/mmol with placebo (P<0.05).

*Agent not available in the United States (US).
Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, I=international, MC=multi-center, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RR=relative risk, SA=sub-analysis, SB=single blind, XO=crossover study
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ARB=angiotensin II receptor blocker, β-blocker=β-adrenergic blocking agent, CABG=coronary artery bypass graft, DBP=diastolic blood pressure, EF=ejection fraction, eGFR=estimated glomerular filtration rate, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, LVEF=left ventricular ejection fraction, MRI=magnetic resonance imaging, NYHA=New York Heart Association, SBP=systolic blood pressure, SF-36=short form health survey, TIA=transient ischemic attack, UACR=urinary albumin: creatinine ratio

Additional Evidence

Dose Simplification
Ludbrook et al. evaluated the differences in blood pressure control and adverse events with spironolactone 300 to 400 mg administered either once-daily in divided doses.[52] Both administration schedules were associated with comparable systolic and diastolic blood pressure reductions. None of the regimens reduced the incidence of adverse effects (85% in both groups).

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 11. Relative Cost of the Mineralocorticoid (Aldosterone) Receptor Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Eplerenone	tablet	Inspra®*	$$$$	$$$
Spironolactone	tablet	Aldactone®*	$$-$$$$	$-$$
Spironolactone and hydrochlorothiazide	tablet	Aldactazide®*	$$-$$$	$

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

X. Conclusions

The mineralocorticoid (aldosterone) receptor antagonists are approved for the treatment of hypertension.[1-6] Eplerenone is also indicated to improve survival in patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction.[4] Spironolactone is approved for the management of hyperaldosteronism, hypokalemia, and edema associated with congestive heart failure, cirrhosis, or the nephrotic syndrome.[5] It is also indicated for patients with severe heart

failure (NYHA class III – IV) to increase survival, and to reduce the need for hospitalization for heart failure when used in addition to standard therapy. All of the products are available in a generic formulation.

There are several national and international guidelines that provide recommendations regarding the use of the mineralocorticoid (aldosterone) receptor antagonists. For the treatment of heart failure, an aldosterone antagonist is recommended in patients with severe symptoms (NYHA class III to IV) and an LVEF ≤35%.[10-12] Therapy should be in addition to an ACE inhibitor (or angiotensin II receptor antagonist) and β-blocker. An aldosterone antagonist is also recommended following a myocardial infarction in patients with an LVEF ≤40% who also have either diabetes or heart failure.[7-9,11,62,67-68] Once again, therapy should be in addition to an ACE inhibitor and β-blocker. Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[13-14,16,20] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[15,17] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[15,17] The guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[13-20] Most patients will require more than one antihypertensive agent to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[15,17] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations. For the treatment of cirrhosis and ascites, spironolactone is recommended as first-line therapy in addition to sodium restriction.[22-23] Spironolactone is also recommended for the treatment of patients with unilateral primary aldosteronism (in lieu of surgery) and in those with bilateral adrenal disease.[21,66] Eplerenone is considered an alternative treatment option, especially in men who experience erectile dysfunction and gynecomastia with spironolactone therapy.[21,66]

Eplerenone and spironolactone have been shown to reduce cardiovascular morbidity and mortality in patients with heart failure when added to standard therapy.[28,32] These agents have also been shown to effectively lower blood pressure.[25-26,35-39,40-42,55,59,62] Only one trial in hypertensive patients included both eplerenone and spironolactone.[39] Both products significantly decreased blood pressure compared to placebo; however, statistical analyses were not performed among the two agents. The authors noted that there was a greater reduction in blood pressure with spironolactone 50 mg twice daily compared to eplerenone 50 mg twice daily. This information suggests that eplerenone may only be 50%–75% as potent as spironolactone. Several studies in diabetic and non-diabetic patients with renal disease have demonstrated a reduction in proteinuria with the addition of spironolactone to existing ACE inhibitor and/or angiotensin II receptor antagonist therapy.[44,47-51,56,61,63]

In general, adverse events are similar with the mineralocorticoid (aldosterone) receptor antagonists and both agents can increase serum potassium levels. While eplerenone is a selective aldosterone receptor antagonist, spironolactone may also antagonize glucocorticoid, progesterone and androgen receptors.[1-3] Consequently, there is an increased risk of steroid-related adverse effects with spironolactone (e.g., gynecomastia, impotence, menstrual abnormalities).

There is insufficient evidence to support that one brand mineralocorticoid (aldosterone) receptor antagonist 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 mineralocorticoid (aldosterone) receptor antagonists 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 mineralocorticoid (aldosterone) receptor antagonist 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 Renin Inhibitors
AHFS Class 243240
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I. Overview

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[7] Excessive activity of the RAAS may lead to hypertension, as well as fluid and electrolyte disorders. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is the first and rate-limiting step of the RAAS.[7-9] Angiotensin I is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II may also be generated through other pathways (angiotensin I convertase). Through a negative feedback mechanism, angiotensin II inhibits renin release.[4] Angiotensin II can increase blood pressure by direct vasoconstriction, as well as through actions on the brain and autonomic nervous system. In addition, angiotensin II induces aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption.[9] Angiotensin II exerts other detrimental effects, including ventricular hypertrophy, remodeling and myocyte apoptosis.

Aliskiren is the only renin inhibitor that is currently available and it is approved for the treatment of hypertension.[1-6] It decreases plasma renin activity and inhibits the conversion of angiotensinogen to angiotensin I. It is unknown if aliskiren affects other RAAS components, such as ACE or non-ACE pathways. Aliskiren is available as a single entity product, as well as in combination with hydrochlorothiazide or valsartan.[4-6] Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride. Valsartan is an angiotensin II receptor antagonist, which blocks the binding of angiotensin II to the AT_1 receptor in various tissues.

The renin inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products currently available. Tekamlo® (aliskiren and amlodipine) is a fixed-dose combination product that was added to Medicaid's drug file in September 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 September 2008.

Table 1. Renin Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Aliskiren	tablet	Tekturna®	none
Aliskiren and hydrochlorothiazide	tablet	Tekturna HCT®	none
Aliskiren and valsartan	tablet	Valturna®	none

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

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the renin inhibitors are summarized in Table 2. For a more comprehensive overview of the pharmacologic management of hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Renin Inhibitors

Clinical Guideline	Recommendation(s)
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension**	• Thiazide-type diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular

Clinical Guideline	Recommendation(s)
Management[33] (2009)	risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • Several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an ARB or a CCB, and in recent large-scale trials for the ACE inhibitor/CCB combination. The ARB/CCB combination also appears to be rational and effective. These combinations can be recommended for priority use. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment. • Combination treatment is commonly needed to effectively lower blood pressure in diabetic patients. A renin–angiotensin receptor blocker should always be included because of the evidence of its protective effect against initiation or progression of nephropathy. • The available evidence justifies the use of aliskiren in hypertension, especially in combination with other agents. This is also supported by the favorable tolerance profile of aliskiren.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[12] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, and the combination is likely to be well tolerated. • The use of renin inhibitors was not addressed in this guideline.
National Institute for Health and Clinical Excellence	• Initial therapy in patients ≥55 years should be a calcium-channel blocking agent (CCB) or a thiazide diuretic, and in patients <55 years

Clinical Guideline	Recommendation(s)
(NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update**[13] **(2006)**	initial therapy should be an angiotensin-converting enzyme (ACE) inhibitor. If a second medication is required and the initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • The use of renin inhibitors was not addressed in this guideline.
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)**[10] **(2004)**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • The use of renin inhibitors was not addressed in this guideline.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease**[16] **(2004)**	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30mL/min/1.73m^2. (Note: Tekturna HCT® is not recommended in patients with a creatinine clearance of ≤30 mL/min.^{2}) Long-acting diuretics and use of diuretics with other antihypertensive agents should be considered to increase patient adherence. • The use of renin inhibitors was not addressed in this guideline.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension**[11] **(2003)**	• If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • The use of renin inhibitors was not addressed in this guideline.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[15] **(2003)**	• Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB or ARB plus diuretic. • The use of renin inhibitors was not addressed in this guideline.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[14] **(2010)**	• Multiple drug therapy is generally required to achieve blood pressure goals. • The use of renin inhibitors was not addressed in this guideline.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the renin 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 Renin Inhibitors[1-6]

Indication	Aliskiren	Aliskiren/ Hydrochlorothiazide	Aliskiren/ Valsartan
Hypertension			
Treatment of hypertension	✔ *	✔ *	✔ *

*Alone or in combination with other antihypertensive agents.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Renin Inhibitors[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aliskiren	2.5	47-51	Liver, minor	Renal (<1) Feces (91)	40
Aliskiren and hydrochlorothiazide	A: 2.5 H: 50-75	A: 47-51 H: 40-68	A: Liver, minor	A: Renal (<1) Feces (91) H: Renal (>95)	A: 40 H: 6-15
Aliskiren and valsartan	A: 2.5 V: 25	A: 47-51 V: 95	A: Liver, minor V: Liver, minor	A: Renal (<1) Feces (91) V: Renal (7-13) Feces (83)	A: 40 V: 6-9

A=aliskiren, H=hydrochlorothiazide, V=valsartan

V. Drug Interactions

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

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

Generic Name(s)	Significance Level	Interaction	Mechanism
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics may induce hypokalemia and increase the risk of torsades de pointes.
Hydrochlorothiazide	1	Lithium	Decreased lithium clearance may occur with thiazide use, which may lead to increased serum lithium levels and possibly lithium toxicity.
Valsartan	1	Potassium-sparing diuretics	The combination of valsartan and potassium-sparing diuretics may increase serum potassium levels, leading to additive or synergistic effects.

Generic Name(s)	Significance Level	Interaction	Mechanism
Aliskiren	2	ACE inhibitors	Aliskiren has been associated with infrequent increases in serum potassium of >5.5 meq/L (0.9% vs 0.6% with placebo). When aliskiren was used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Use caution when aliskiren is given concomitantly with ACE inhibitors. Routine monitoring of electrolytes and renal function is indicated in this population.
Aliskiren	2	Cyclosporine	Concurrent use of aliskiren and cyclosporine may result in increased aliskiren exposure and plasma concentrations.
Aliskiren	2	Potassium preparations	Hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest, may occur with the combination of aliskiren and potassium preparations.
Aliskiren	2	Potassium-sparing diuretics	The risk of hyperkalemia may be increased when aliskiren is coadministered with potassium-sparing diuretics. Decreased aldosterone activity by aliskiren may function synergistically with potassium conservation by potassium-sparing diuretics leading to the development of hyperkalemia.
Hydrochlorothiazide	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia, hyperuricemia and hypotension.
Hydrochlorothiazide	2	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.
Valsartan	2	ACE inhibitors	Coadministration of valsartan and ACE inhibitors may be associated with an increased risk of renal dysfunction and/or hyperkalemia.
Valsartan	2	Lithium	Valsartan may decrease lithium renal excretion by enhancing its reabsorption. Lithium levels may increase, resulting in an increase in pharmacologic and toxic effects of lithium.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the renin inhibitors are listed in Table 6. The boxed warning for aliskiren is listed in Table 7.

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

Adverse Events	Aliskiren	Aliskiren/ Hydrochlorothiazide	Aliskiren/ Valsartan
Cardiovascular			
Hypotension	<1	<1	<1
Peripheral edema	✔	✔	✔
Central Nervous System			
Dizziness	>1	2	>1
Fatigue	>1	>1	3
Headache	>1	>1	>1
Paresthesia	-	-	✔
Restlessness	-	✔	-
Seizure	✔	✔	✔
Vertigo	1	1	1
Dermatologic			
Erythema multiforme	-	✔	-
Exfoliative dermatitis	-	✔	-
Photosensitivity	-	✔	-
Rash	1	1	1
Stevens-Johnson syndrome	-	✔	-
Toxic epidermal necrolysis	-	✔	-
Urticaria	-	✔	-
Endocrine and Metabolic			
Gout	<1	<1	<1
Gastrointestinal			
Abdominal pain	✔	✔	✔
Cramping	-	✔	-
Diarrhea	2	2	2
Dyspepsia	✔	✔	✔
Gastric irritation	-	✔	-
Gastroesophageal reflux	✔	✔	✔
Genitourinary			
Glycosuria	-	✔	-
Impotence	-	-	✔
Urinary tract infection	-	-	1
Hematologic			
Agranulocytosis	-	✔	-
ALT increased	-	1	-
Anemia	✔	-	✔
Aplastic anemia	-	✔	-
Hematocrit decreased	✔	✔	✔
Hemoglobin decreased	✔	✔	✔
Hemolytic anemia	-	✔	-
Leukopenia	-	✔	-
Thrombocytopenia	-	✔	-
Laboratory Test Abnormalities			
Alanine aminotransaminase increased	-	1	-
Blood urea nitrogen increased	7	12	<1
Creatine kinase increased	1	-	-
Hyperglycemia	-	✔	-

Adverse Events	Aliskiren	Aliskiren/ Hydrochlorothiazide	Aliskiren/ Valsartan
Hyperkalemia	1	1	4
Hypokalemia	-	2	-
Serum creatinine increased	7	1	<1
Uric acid increased	<1	<1	<1
Musculoskeletal			
Arthralgia	-	1	-
Asthenia	-	1	✔
Back pain	>1	>1	>1
Muscle cramps	-	-	✔
Muscle spasm	-	✔	-
Myositis	<1	-	-
Rhabdomyolysis	<1	-	-
Weakness	-	✔	-
Renal			
Interstitial nephritis	-	✔	-
Renal dysfunction	-	✔	-
Renal failure	-	✔	-
Renal stones	<1	<1	<1
Respiratory			
Cough	1	1	>1
Influenza	-	2	1
Nasopharyngitis	✔	>1	3
Pharyngitis	-	-	✔
Respiratory distress	-	✔	-
Sinusitis	-	-	✔
Upper respiratory infection	>1	>1	>1
Other			
Allergic reaction	-	-	✔
Angioedema	✔	✔	✔
Blurred vision	-	✔	-
Edema (face, hands, or whole body)	<1	<1	<1
Fever	-	✔	-
Jaundice	-	✔	-
Necrotizing angiitis	-	✔	-
Pancreatitis	-	✔	-
Periorbital edema	✔	✔	✔
Purpura	-	✔	-
Xanthopsia	-	✔	-

✔ Percent not specified.
\- Event not reported.

Table 7. Boxed Warning for Aliskiren Products[1]

WARNING
When pregnancy is detected, discontinue aliskiren as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

VII. Dosing and Administration

The usual dosing regimens for the renin inhibitors are listed in Table 8.

Table 8. Usual Dosing Regimens for the Renin Inhibitors[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aliskiren	Hypertension: Initial, 150 mg once daily; may increase daily dose to 300 mg if blood pressure not adequately controlled	Safety and efficacy in children have not been established.	Tablet: 150 mg 300 mg
Aliskiren and hydrochlorothiazide	Hypertension: Initial therapy: 150 mg-12.5 mg once daily; maximum, 300 mg-25 mg once daily Add-on therapy: A patient whose blood pressure is not adequately controlled with aliskiren alone or hydrochlorothiazide alone may be switched to combination therapy. The recommended starting dose is 150 mg-12.5 mg once daily; maximum, 300 mg-25 mg once daily Replacement therapy: substitute for individually titrated components	Safety and efficacy in children have not been established.	Tablet: 150 mg-12.5 mg 150 mg-25 mg 300 mg-12.5 mg 300 mg-25 mg
Aliskiren and valsartan	Hypertension: Initial therapy: 150 mg-160 mg once daily; maximum, 300 mg-320 mg once daily Add-on therapy: A patient whose blood pressure is not adequately controlled with aliskiren alone or valsartan alone may be switched to combination therapy. The recommended starting dose is 150 mg-160 mg once daily; maximum, 300 mg-320 mg once daily Replacement therapy: substitute for individually titrated components	Safety and efficacy in children have not been established.	Tablet: 150 mg-160 mg 300 mg-320 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the renin inhibitors are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Renin Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypertension				
Oh et al.[17] (2007) Aliskiren 150 mg, 300 mg or 600 mg QD vs placebo	DB, MC, PC, PG, RCT Men and women ≥18 years (mean age 53 years) with mild-to-moderate essential hypertension (DBP ≥95 and <110 mm Hg)	N=672 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, 24-hour ABPM, proportion achieving a successful treatment response (defined as DBP <90 mm Hg or ≥10 mm Hg pressure reduction from baseline) or blood pressure control (defined as <140/90 mm Hg), plasma renin activity and concentration, safety and tolerability	Primary: All three doses investigated provided significantly greater reductions in mean sitting DBP from baseline compared to placebo (all P<0.0001). The mean sitting DBP reductions were 10.3 mm Hg with 150 mg, 11.1 mm Hg with 300 mg and 12.5 mm Hg with 600 mg compared to 4.9 mm Hg with placebo. Secondary: All three doses provided significantly greater reductions in mean sitting SBP from baseline compared to placebo (all P<0.0001). The mean sitting SBP reductions were 13.0 mm Hg with 150 mg, 14.7 mm Hg with 300 mg and 15.8 mm Hg with 600 mg compared to 3.8 mm Hg with placebo. Reduction in the 24-hour ABPM was significantly greater in all doses of aliskiren compared to placebo (n=216; all P<0.0001). Reductions in mean ambulatory DBP and SBP were consistent across the 24-hour dosing interval with all aliskiren doses. The proportion of patients achieving a successful treatment response was 59.3% with aliskiren 150 mg, 63.3% with 300 mg and 69.3% with 600 mg compared to 36.2% with placebo (all P<0.0001). The proportion of patients achieving blood pressure control was 35.9% with 150 mg, 41.6% with 300 mg and 46.4% with 600 mg compared to 20.3% with placebo (all P<0.0001). Plasma renin activity decreased 79.5% with 150 mg, 81.1% with 300 mg and 75.0% with 600 mg compared to an increase of 19.5% with placebo. Aliskiren resulted in dose-dependent increases from baseline in renin concentrations (51.5%, 101.6%, and 228.5% for 150, 300 and 600 mg, respectively). Renin concentrations were almost unchanged with placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kushiro et al.[18] (2006) Aliskiren 75, 150 or 300 mg QD vs placebo	DB, MC, PC, PG, RCT Japanese men and women between the ages of 20 and 80 years with essential hypertension (mean sitting DBP of ≥90 mm Hg and <110 mm Hg during the run-in period and ≥95 mm Hg and <110 mm Hg at baseline)	N=455 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean trough sitting SBP, proportion of patients responding to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg decrease in mean sitting DBP from baseline), dose-response relationship, safety	Primary: All three aliskiren doses provided significantly greater reductions in mean sitting DBP from baseline compared to placebo. The placebo-corrected reductions in mean sitting DBP were 4.0 mm Hg with 75 mg aliskiren, 4.5 mm Hg with 150 mg and 7.5 mm Hg with 300 mg (all P<0.0005). Secondary: The mean sitting SBP reductions were significantly lower with all aliskiren doses when compared to placebo. The placebo-corrected reductions in mean sitting SBP were 5.7 mm Hg with 75 mg aliskiren, 5.9 mm Hg with 150 mg and 11.2 mm Hg with 300 mg (all P<0.001). The proportion of responders at study end point was 47.8% with aliskiren 75 mg, 48.2% with 150 mg and 63.7% with 300 mg compared to 27.8% with placebo (all P<0.005). Dose-response analysis showed that the relationship between reductions in mean sitting DBP and SBP and aliskiren dose was almost linear. However, further analyses revealed that a pattern of similar reductions with aliskiren 75 and 150 mg and greater reductions with aliskiren 300 mg was a better fit for both mean sitting DBP and SBP. The incidence of drug-related adverse events was comparable between aliskiren (53%-55%) and placebo (50%). There was no evidence of a dose-dependent increase in the incidence of all-causality adverse events at the aliskiren doses evaluated in this study.
Musini et al.[34] (2009) Aliskiren (variable doses) vs placebo	MA Patients ≥18 years of age with mild to moderate essential hypertension (defined as mean sitting diastolic blood pressure ≤95 mm Hg and ≤110 mm Hg at baseline)	N=3,694 (6 trials) 8 weeks	Primary: Changes in dose-related systolic blood pressure (SBP) and diastolic blood pressure (DBP) Secondary: Variability of blood pressure	Primary: Aliskiren monotherapy was more effective than placebo in lowering mean sitting SBP. The additional magnitude of BP lowering minus the placebo effect: aliskiren 75 mg vs placebo -2.94 (95% CI, -4.56 to -1.31); aliskiren 150 mg vs placebo -5.45 (95% CI, -6.46 to -4.43); aliskiren 300 mg vs placebo -8.66 (95% CI, -9.68 to 7.64); aliskiren 600 mg vs placebo -11.36 (95% CI, -13.53 to -9.19). Aliskiren monotherapy was more effective than placebo in lowering mean sitting DBP. The additional magnitude of BP lowering minus the placebo effect: aliskiren 75 mg vs placebo -2.29 (95% CI, -3.31 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(BP), pulse pressure, heart rate, withdrawals due to adverse effects, and rates of specific adverse effects	-1.26); aliskiren 150 mg vs placebo -3.00 (95% CI, -3.65 to -2.34); aliskiren 300 mg vs placebo -4.97 (95% CI, -5.62 to -4.31); aliskiren 600 mg vs placebo -6.57 (95% CI, -7.92 to -5.23). Secondary: No trials reported on pulse pressure at baseline or end point. Two trials recorded baseline heart rate, but no data were provided at week 8. There were no significant differences in withdrawals between placebo and aliskiren at any dose. The relative risk for aliskiren 75 mg vs placebo was 0.97 (95% CI, 0.49 to 1.89); for aliskiren 150 mg vs placebo was 1.01 (95% CI, 0.61 to 1.69); for aliskiren 300 mg vs placebo was 0.91 (95% CI, 0.57 to 1.47) and for aliskiren 600 mg vs placebo was 0.63 (9% CI, 0.21 to 1.89). One trial reported on the incidence of dry cough: placebo (1.1%); aliskiren 75 mg (1.1%); aliskiren 150 mg (2.8%); aliskiren 300 mg (0.6%). No trials reported angioedema. The BP lowering efficacy of aliskiren 150 mg vs 75 mg, as well as aliskiren 600 mg vs 300 mg was not significantly different. Aliskiren 300 mg significantly lowered both systolic and diastolic BP as compared to 150 mg (SBP: -2.97; 95% CI, -3.99 to -1.95; DBP: -1.66; 95% CI, -2.32 to -1.0).
Schmieder et al.[29] (2009) Aliskiren 150 to 300 mg QD (with optional addition of amlodipine 5 to 10 mg QD) vs HCTZ 12.5 to 25 mg QD (with	DB, AC, RCT Adults with essential hypertension	N=1,124 12 months	Primary: Safety and change in mean sitting diastolic blood pressure (DBP) Secondary: Change in mean sitting systolic blood pressure (SBP)	Primary: The proportion of patients who experienced adverse events during the 6-week placebo-controlled period was similar in the aliskiren monotherapy, hydrochlorothiazide monotherapy, and placebo groups (26.4%, 24.5%, and 28.5%, respectively). During the 52-week double-blind treatment period, adverse events were reported by a similar proportion of patients receiving the aliskiren and hydrochlorothiazide regimens. Most adverse events were mild or moderate in intensity. At week 26, the aliskiren regimen provided significantly greater reductions from baseline in DBP compared to hydrochlorothiazide (-14.2

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
optional addition of amlodipine 5 to 10 mg QD) vs placebo for 6 weeks, then randomized to either aliskiren 300 mg QD or HCTZ 25 mg QD				mm Hg and -13.0 mm Hg, respectively; P<0.05) The greater reduction in DBP with the aliskiren regimen compared with the hydrochlorothiazide regimen was maintained at week 52 (-16.0 mm Hg and -15.0 mm Hg, respectively; P<0.05). Secondary: At week 26, the aliskiren regimen provided significantly greater reductions from baseline in SBP compared to hydrochlorothiazide (-20.3 mm Hg and -18.6 mm Hg, respectively; P<0.05). Reductions in SBP at week 52 were not inferior to those of hydrochlorothiazide (-22.1 mm Hg and -21.2 mm Hg, respectively; P<0.0001 for non-inferiority).
Littlejohn et al.[40] (2009) Aliskiren 150 to 300 mg and amlodipine 5 to 10 mg QD HCTZ may be added if additional blood pressure control was required.	OL, MC Patients ≥18 years of age with essential hypertension (msDBP ≥90 mm Hg and <110 mm Hg)	N=556 12 months	Primary: Safety and tolerability Secondary: BP-lowering efficacy	Primary: Long-term treatment with aliskiren/amlodipine was generally well tolerated. In total, 76.3% of patients reported at least one adverse event (AE). The majority were mild or moderate in severity and transient. The most frequently reported AEs were peripheral edema, upper respiratory tract infection, headache and bronchitis. Peripheral edema was reported in 20.5% of patients who received aliskiren/amlodipine and in 14.0% of patients who received aliskiren/amlodipine/HCTZ. Edema was reported as mild in 59.5%, moderate in 33.3% and severe in 7.1% of patients. Secondary: At week 2, treatment with aliskiren/amlodipine led to a mean reduction in BP of 13.5/8.3 mm Hg. At week 10, there was a mean reduction in BP of 23.5/15.1 mm Hg. BP reductions were sustained from week 10 until the end of the study. At week 54, aliskiren/amlodipine decreased mean BP from 153.5/97.6 mm Hg at baseline to 129.4/82.2 mm Hg (P<0.001). The BP control rate was 74.3% with aliskiren/amlodipine at week 54.
Villamil et al.[19] (2007)	DB, MC, PC, RCT Men and women	N=2,776 8 weeks	Primary: Change in mean sitting DBP	Primary: Aliskiren monotherapy significantly reduced mean sitting DBP (P=0.0002). Only the aliskiren 150 and 300 mg doses were more effective

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aliskiren 75 to 300 mg QD vs HCTZ 6.25 to 25 mg QD vs aliskiren and HCTZ (every dose combination except aliskiren 300 mg and HCTZ 6.25 mg) QD (single entity products) vs placebo	≥18 years with mild-to-moderate essential hypertension		Secondary: Change in mean sitting SBP, dose-response efficacy for all treatment groups, proportion achieving a successful response (DBP <90 mm Hg or ≥10 mm Hg), proportion achieving blood pressure control (<140/90 mm Hg), plasma renin activity, renin concentrations, safety	than placebo (P=0.09 for aliskiren 75 mg). HCTZ monotherapy significantly reduced DBP from baseline (all, P<0.01 vs placebo). All combinations were more effective than placebo (P<0.0001) with reductions in DBP ranging from 10.4 to 14.3 mm Hg. Most combination regimens were more effective than monotherapy with the individual components (exceptions were aliskiren 150 mg plus HCTZ 6.25 mg vs monotherapy, and aliskiren 75 mg plus HCTZ 12.5 mg vs HCTZ monotherapy). Secondary: After 8 weeks of therapy, aliskiren 150 and 300 mg regimens (both P<0.0001) were more effective than placebo in lowering mean sitting SBP, but the 75 mg dose was not (P=0.151). Combination therapy was consistently more effective in reducing SBP than monotherapy with the individual components, with the exception of aliskiren 75 mg plus HCTZ 12.5 vs HCTZ monotherapy. Reductions in SBP with combination therapy ranged from 14.3 to 21.2 mm Hg. Blood pressure reductions were related to the doses of both aliskiren and HCTZ. Responder rates were significantly higher with aliskiren 300 mg (63.9%; P=0.0005), HCTZ 12.5 and 25 mg (60.6% and 59.0%, respectively; both P<0.02) and all combination doses (58.4% to 80.6%; all P<0.05) than placebo (45.8%). Responder rates for all combinations of aliskiren plus HCTZ 25 mg, and aliskiren 300 mg plus HCTZ 12.5 mg were higher than both monotherapies (P<0.05), while aliskiren 75 mg plus HCTZ 12.5 mg and aliskiren 150 mg plus HCTZ 12.5 mg were more effective than their respective aliskiren monotherapies (P<0.05). In the aliskiren and HCTZ monotherapy groups, only aliskiren 300 mg led to statistically significantly greater control rates than placebo (46.7% vs 28.1%; P=0.0001). Control rates for all combinations, with the exception of aliskiren 75 mg plus HCTZ 6.25 mg, were higher than placebo (all P<0.02). There was a trend towards improved control rates with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				combination therapy (37.4% to 59.5%) compared to aliskiren monotherapy (29.0% to 46.7%) or HCTZ monotherapy (32.5% to 37.8%). Combinations utilizing the higher doses of one or both drugs (aliskiren 75-300 mg with HCTZ 25 mg or aliskiren 150-300 mg with HCTZ 12.5 mg) yielded control rates that were significantly higher than monotherapy with either component. While all doses of aliskiren decreased plasma renin activity and all doses of HCTZ increased plasma renin activity, combination therapy resulted in decreased plasma renin activity of 46.1% to 63.5%. Renin concentrations increased in all monotherapy and combination regimens with the exception of HCTZ 6.25 and 12.5 mg. All active treatments were well tolerated with 37.3% to 39.2% of patients experiencing adverse events with aliskiren monotherapy, 38.7% to 42.0% with HCTZ monotherapy, 34.6% to 45.3% with aliskiren plus HCTZ, and 44% with placebo. Hypokalemia (serum potassium <3.5 mmol/L) occurred with the highest frequency with HCTZ 12.5 and 25 mg (3.9% and 5.2%, respectively). When administered in combination with aliskiren, the frequency of hypokalemia was 0.7% to 2.0% with HCTZ 12.5 mg and 2.2% to 3.4% with HCTZ 25 mg.
Jordan et al.[23] (2007) Aliskiren 150 to 300 mg QD added to existing HCTZ therapy (single entity products) vs amlodipine 5 to 10 mg QD added to existing HCTZ therapy (single entity products)	DB, DD, MC, PG, RCT Obese men and women (BMI ≥30 kg/m^2) ≥18 years with essential hypertension (mean sitting DBP 95-109 mm Hg and SBP <180 mm Hg) who had not responded to 4 weeks of treatment with HCTZ 25 mg	N=489 12 weeks	Primary: Change in mean sitting DBP with aliskiren 300 mg plus HCTZ vs HCTZ alone at 8 weeks Secondary: Comparisons of mean sitting DBP and SBP with aliskiren plus HCTZ vs the other treatment groups, percentage of	Primary: Aliskiren 300 mg added to HCTZ 25 mg significantly reduced mean sitting DBP compared with HCTZ alone at week 8 (mean difference, –4.0; P<0.0001). Secondary: Aliskiren 300 mg added to HCTZ caused numerically larger reductions in mean sitting DBP and SBP compared with amlodipine 10 mg plus HCTZ and irbesartan 300 mg plus HCTZ at week 8, but there were no statistically significant differences between treatment groups (P>0.05). Responder rates were significantly higher with aliskiren plus HCTZ than HCTZ alone at week 8 (P=0.0193) and week 12 (P=0.004) but comparable to responder rates observed with amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs irbesartan 150 to 300 mg QD added to existing HCTZ therapy (single entity products) vs HCTZ 25 mg QD (existing therapy)			responders (mean sitting DBP <90 mm Hg or ≥10 mm Hg reduction from baseline), proportion of patients achieving blood pressure control (mean sitting blood pressure <140/90 mm Hg), plasma renin activity, safety and tolerability	The proportion of patients achieving blood pressure control was significantly higher with aliskiren plus HCTZ than HCTZ alone at week 8 (P=0.0005) and week 12 (P=0.0001) but not statistically different than amlodipine plus HCTZ (P>0.05) and irbesartan plus HCTZ (P>0.05). Plasma renin activity significantly increased (P<0.05) during 4 weeks of HCTZ monotherapy. Combination with aliskiren neutralized this increase and led to an overall significant reduction in plasma renin activity compared with pretreatment baseline (P<0.05) whereas amlodipine and irbesartan led to further significant increases (P<0.05). All of the study treatments were generally well tolerated. Amlodipine plus HCTZ (45.2%) was associated with a higher incidence of adverse events than the other treatment groups (36.1% to 39.3%), largely due to a higher rate of peripheral edema (11.1% vs 0.8% to 1.6%).
Nickenig et al.[39] (2008) Aliskiren/HCTZ 300/25 mg QD (fixed-dose combination) vs aliskiren/HCTZ 300/12.5 mg QD (fixed-dose combination) vs aliskiren 300 mg QD (existing therapy)	RCT, DB, MC Patients with hypertension and an inadequate response to aliskiren (mean sitting diastolic BP >90 and ≤110 mm Hg following 4 weeks of aliskiren 300 mg)	N=880 8 weeks	Primary: Changes in mean sitting systolic/diastolic blood pressure (msSBP/DBP); rates of blood pressure (BP) control (<140/90 mm Hg)	Primary: The change in mean sitting systolic/diastolic BP (msSBP/DBP) from baseline were analyzed for the intent-to-treat population. Results. Treatment with aliskiren/HCTZ 300/25 mg and 300/12.5 mg led to significantly greater reductions in msSBP/DBP from baseline (15.9/11.0 mm Hg and 13.5/10.5 mm Hg, respectively) than aliskiren 300 mg (8.0/7.4 mm Hg; both P<0.001). Rates of BP control were significantly higher with aliskiren/HCTZ 300/25 mg (60.2%) and 300/12.5 mg (57.9%) than with aliskiren 300 mg (40.9%; both P<0.001). Patients treated with aliskiren/HCTZ or aliskiren monotherapy demonstrated similar tolerability.
Blumenstein et al.[37]	RCT, DB, MC	N=722	Primary: Changes in mean	Primary: The mean reductions in msSBP/DBP from baseline with aliskiren/HCTZ

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Aliskiren/HCTZ 300/25 mg QD (fixed-dose combination) vs aliskiren/HCTZ 150/25 mg QD (fixed-dose combination) vs HCTZ 25 mg (existing therapy)	Patients with hypertension and an inadequate response to HCTZ (mean sitting diastolic BP >90 and ≤110 mm Hg following 4 weeks of HCTZ 25 mg)	8 weeks	sitting systolic/diastolic blood pressure (msSBP/DBP), proportion of patients achieving BP control (mean sitting BP <140/90 mm Hg) and BP response rates (msDBP <90 mm Hg or a ≥10 mm Hg decrease from baseline)	300/25 mg and 150/25 mg were significantly greater than those achieved with HCTZ monotherapy (all P<0.001). Rates of BP control were significantly higher with aliskiren/HCTZ 300/25 mg and 150/25 mg than with HCTZ monotherapy (both P<0.001). Aliskiren/HCTZ 300/25 mg provided significantly greater reductions in msSBP/DBP and rates of BP control than the aliskiren/HCTZ 150/25 mg dose (all P<0.05). BP response rates were significantly higher with aliskiren/HCTZ 300/25mg (78.5%) and aliskiren/HCTZ 150/25 mg (67.4%) than with HCTZ monotherapy (47.1%; P<0.001 for both comparisons). All treatments were generally well-tolerated and the proportion of patients experiencing adverse events was similar across treatment groups. The majority of adverse events were mild and transient. Adverse events reported in >2% of patients were nasopharyngitis, dizziness, back pain and vertigo. The proportion of patients with serum potassium <3.5 mmol/L was lower with aliskiren/ HCTZ (1.3% to 2.2%) than HCTZ monotherapy (3.4%). Hyperkalemia (serum potassium >5.5 mmol/L) was observed in only one patient receiving aliskiren/HCTZ and two patients in the HCTZ monotherapy group. No patient had increases in serum creatinine above the pre-specified clinically significant threshold.
Gradman et al.[24] (2005) Aliskiren 150 to 600 mg QD vs irbesartan 150 mg QD	DB, MC, PC, PG, RCT Men and women, age 18 years or older, with mild-to-moderate essential hypertension (mean sitting DBP ≥95 mm Hg and <110 mm Hg)	N=652 8 weeks	Primary: Change in mean sitting DBP and SBP Secondary: Proportion of patients achieving blood pressure control (<140/90 mm Hg), safety	Primary: Decreases in mean sitting DBP at 8 weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough DBP for aliskiren 150, 300 and 600 mg were 9.3, 11.8, and 11.5 mm Hg, respectively, versus 6.3 mm Hg for placebo. Decreases in mean sitting SBP at 8 weeks were significantly greater with all doses of aliskiren compared to placebo (P<0.001). The least-squares mean reductions in trough SBP for aliskiren 150, 300 and 600 mg were 11.4, 15.8, and 15.7 mm Hg, respectively, versus 5.3 mm Hg for placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				The antihypertensive effect of aliskiren 150 mg was comparable to irbesartan 150 mg with reductions of 8.9 and 12.5 mm Hg for mean sitting DBP and SBP, respectively. Aliskiren 300 and 600 mg produced significantly greater mean sitting DBP reductions than irbesartan 150 mg (P<0.05). While the reductions in mean sitting SBP were greater with aliskiren 300 and 600 mg than irbesartan 150 mg, these differences were not statistically significant). Secondary: The percentage of patients achieving blood pressure control was significantly greater with all doses of aliskiren (37.8%-150 mg, 50.0%-300 mg, 45.7%-600 mg) and irbesartan (33.8%) compared to placebo (20.8%; P<0.05). More patients on aliskiren 300 and 600 mg achieved blood pressure control compared to irbesartan (P<0.05). Drug-related adverse events for both aliskiren and irbesartan were comparable to placebo and the most commonly reported adverse events were headache, dizziness, and diarrhea. The number of patients discontinuing therapy was similar in all groups.
Obrien et al.[22] (2007) Aliskiren 150 mg QD for 3 weeks, then HCTZ 25 mg QD was added for an additional 3 weeks (if ABPM remained ≥135/85 mm Hg) vs irbesartan 150 mg QD for 3 weeks, then aliskiren 75 mg QD added for	3 OL studies Men and women 18-80 years with ambulatory SBP ≥140 and ≤180 mm Hg without treatment	N=67 6 to 9 weeks	Primary: Change in daytime systolic ABPM with combination therapy compared with monotherapy Secondary: Change in daytime diastolic ABPM, nighttime systolic and diastolic ABPM, daytime and nighttime heart rates, plasma renin activity	Primary: Aliskiren coadministered with HCTZ (P=0.0007) or ramipril (P=0.03) led to significantly greater reductions in daytime systolic ABPM compared to monotherapy. There was a trend for a reduction in daytime systolic ABPM with the addition of aliskiren to irbesartan; however, this trend was not statistically significant. Secondary: Aliskiren plus HCTZ significantly lowered daytime diastolic ABPM compared to aliskiren monotherapy (P=0.0006). Changes in nighttime systolic and diastolic ABPM followed similar trends but did not achieve statistical significance (P=0.06 and P=0.09, respectively). No changes in heart rate were observed with either aliskiren regimen. Aliskiren added to irbesartan did not significantly change diastolic ABPM compared to irbesartan monotherapy; however, nighttime systolic and diastolic ABPM were significantly reduced (all P<0.05). No changes in heart rate were observed with either irbesartan regimen.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 weeks, then aliskiren 150 mg QD added for 3 weeks vs ramipril 5 mg QD for 3 weeks, then aliskiren 75 mg QD added for 3 weeks, then aliskiren 150 mg QD added for 3 weeks				Mean diastolic ABPM was significantly decreased with the addition of aliskiren 150 mg (P<0.05) but not aliskiren 75 mg to ramipril monotherapy. Both aliskiren doses significantly decreased nighttime systolic and diastolic ABPM (all P<0.05). No changes in heart rate were observed with either ramipril regimen. Aliskiren alone significantly inhibited plasma renin activity by 65% (P<0.0001), while ramipril and irbesartan monotherapy increased renin activity by 90% and 175%, respectively. When aliskiren was coadministered with HCTZ, ramipril or irbesartan, plasma renin activity remained similar to baseline levels or decreased.
Strasser et al.[20] (2007) Aliskiren 150 to 300 mg QD vs lisinopril 20 to 40 mg QD HCTZ may be added if additional blood pressure control was required.	AC, DB, DD, MC, PG, RCT Men and women with uncomplicated severe hypertension (mean sitting DBP 105-119 mm Hg)	N=183 8 weeks	Primary: Safety Secondary: Change in mean sitting DBP and SBP, percentage of responders	Primary: Both active treatments were well tolerated with an incidence of adverse events of 32.8% for aliskiren and 29.3% for lisinopril. The proportion of patients discontinuing treatment due to adverse events was 3.2% for aliskiren and 3.4% for lisinopril. The most frequently reported adverse events in both groups were headache, nasopharyngitis and dizziness. Secondary: Aliskiren showed similar reductions from baseline to lisinopril in mean sitting DBP (–18.5 vs –20.1 mm Hg) and SBP (–20.0 and –22.3 mm Hg). Responder rates were 81.5% with aliskiren and 87.9% with lisinopril. Approximately half of patients required the addition of HCTZ to achieve blood pressure control (53.6% for aliskiren and 44.8% for lisinopril).
Stanton et al.[25] (2003) Aliskiren 37.5 to 300 mg QD	AC, DB, MC, PG, RCT Men and women 21 to 70 years of age with mild-to-	N=226 4 weeks	Primary: Change in daytime ambulatory SBP Secondary: Changes in clinic	Primary: A clear dose-dependent reduction in daytime ambulatory SBP was observed with increasing aliskiren doses (with mean changes of –0.40 mm Hg with aliskiren 37.5 mg, –5.3 mm Hg with aliskiren 75 mg, –8.0 mm Hg with aliskiren 150 mg, and –11 mm Hg with aliskiren 300 mg; P=0.0002). The change in daytime SBP with losartan 100 mg (–10.9 mm

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs losartan 100 mg QD	moderate hypertension (SBP ≥140 mm Hg)		SBP and DBP, plasma renin activity, plasma aliskiren levels, adverse events	Hg) was significantly different than aliskiren 37.5 mg, but not the other higher aliskiren dosages). Secondary: Clinic SBP and DBP, both in the sitting and standing positions, decreased with aliskiren in a dose-dependent manner, whereas heart rate was unaltered. The decreases in clinic blood pressures were similar for losartan 100 mg and aliskiren 150 and 300 mg. Dose-dependent reductions in plasma renin activity were also observed (median change –55%, –60%, –77%, and –83% with 37.5, 75, 150 and 300 mg aliskiren, respectively; P=0.0008). By contrast, plasma renin activity increased by 110% with losartan 100 mg. Rate of adverse events was 22% with aliskiren 37.5 mg, 35% with aliskiren 75 mg, 25% with aliskiren 150 mg, 23% with aliskiren 300 mg, and 32% with losartan 100 mg. There was no increase in the number of adverse events when increasing the dose of aliskiren.
Uresin et al.[41] (2007) Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD vs aliskiren 150 to 300 mg and ramipril 5 to 10 mg QD	RCT, DB, MC Patients ≥18 years of age with type 1 or type 2 diabetes mellitus and stage 1-2 hypertension (mean sitting diastolic blood pressure (BP) >95 and <110 mm Hg)	N=837 8 weeks	Primary: Change in mean sitting diastolic BP (msDBP) Secondary: Change in mean sitting systolic BP (msSBP), proportion of patients with a successful response to treatment (trough msDBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline), rates of BP control	Primary: Aliskiren, ramipril and aliskiren/ramipril lowered msDBP by 11.3, 10.7, and 12.8 mm Hg, respectively. Treatment with aliskiren/ramipril produced significantly greater reductions from baseline in msDBP than either aliskiren monotherapy (P=0.043) or ramipril monotherapy (P=0.004). Aliskiren 300 mg was statistically non-inferior (P=0.0002) to ramipril 10 mg for the change in msDBP. Secondary: Aliskiren, ramipril and aliskiren/ramipril lowered msSBP by 14.7, 12.0 and 16.6 mm Hg, respectively. Treatment with aliskiren/ramipril produced significantly greater reductions from baseline in msSBP than ramipril monotherapy (P<0.0001), but not aliskiren monotherapy (P=0.088). Aliskiren monotherapy was statistically superior to ramipril for the change in msSBP (P=0.021). The proportion of patients with a successful response to therapy was similar for aliskiren/ramipril (74.1%) and aliskiren (73.1%). The responder rates in both groups were significantly higher (P<0.05) than with ramipril

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			(BP <130/80 mm Hg), changes from baseline in 24-hour ambulatory BP monitoring (ABPM) measurements, and changes in biomarkers (plasma renin concentration [PRC], PRA, aldosterone)	(65.8%). Rates of BP control with aliskiren/ramipril (13.1%) were not significantly different than aliskiren monotherapy (8.2%) or ramipril monotherapy (8.4%). All treatments significantly lowered mean 24-hour ambulatory BP. Aliskiren/ramipril was significantly more effective than ramipril monotherapy in lowering 24-hour mean ambulatory DBP (P=0.034). There was no significant difference in 24-hour ambulatory SBP compared with ramipril monotherapy. Aliskiren significantly reduced PRA from baseline as monotherapy (by 66%, P<0.0001) or in combination with ramipril (by 48%, P<0.0001).
Duprez et al.[36] (2010) AGELESS Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was allowed at week 12 and amlodipine was allowed at week 22 in patients not achieving adequate blood pressure control.	RCT, DB, AC, MC Patients ≥65 years of age with essential hypertension (msSBP ≥140 and <180 mm Hg and mean sitting diastolic BP (msDBP) <110mm Hg)	N=901 36 weeks	Primary: Change in mean seated systolic blood pressure (msSBP) at week 12 Secondary: Change in msSBP at week 36, change in msDBP at week 12 and week 36, percentage of patients who achieved BP control (msSBP/msDBP <140/90 mm Hg in non-diabetic patients and <130/80 mm Hg in diabetic patients) at week 12 and	Primary: At week 12, aliskiren lowered msSBP by 14 mm Hg and ramipril decreased msSBP by 11.6 mm Hg (difference -2.3 mm Hg; 95% CI, -4.3 to -0.3). Aliskiren monotherapy showed statistically non-inferior (P<0.001) and statistically superior (P=0.02) reductions in msSBP compared with ramipril monotherapy. Secondary: At week 22, aliskiren decreased msSBP by 19.6 mm Hg and ramipril decreased msSBP by 17 mm Hg (difference -2.4 mm Hg; 95% CI, -4.5 to -0.3; P=0.03). At week 36, aliskiren decreased msSBP by 20 mm Hg and ramipril decreased msSBP by 18.1 mm Hg (difference -1.9 mm Hg; 95% CI, -4.0 to 0.2; P=0.07). At week 12, aliskiren decreased msDBP by 5.1 mm Hg and ramipril decreased msDBP by 3.6 mm Hg (-1.5 mm Hg; 95% CI, -2.6 to -0.5; P<0.01). At week 22, aliskiren decreased msDBP by 8.2 mm Hg and ramipril decreased msDBP by 7.3 mm Hg (-0.8 mm Hg; 95% CI, -2.0 to 0.3; P=0.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			week 36, percentage of patients who required add-on therapy	At week 36, aliskiren decreased msDBP by 8.2 mm Hg and ramipril decreased msDBP by 7.0 mm Hg (difference -1.2 mm Hg; 95% CI, -2.3 to -0.1; P=0.03). The percentage of patients achieving BP control was significantly greater with aliskiren (42%) compared with ramipril (33%) at week 12 (P<0.01). At week 22, a significantly greater proportion of patients achieved BP control with aliskiren (62%) compared with ramipril (50%; P<0.001). At week 36, similar BP control rates were achieved with aliskiren (59%) and ramipril (51%; P=0.01). By week 36, a significantly greater percentage of patients receiving ramipril than aliskiren required additional HCTZ (56% vs 46%; P<0.01). By week 36, a greater percentage of patients receiving ramipril (16%) compared to aliskiren (12%) required add-on therapy with both HCTZ and amlodipine (P=0.048). More patients receiving aliskiren were receiving monotherapy (42%) than patients receiving ramipril (29%) at week 36.
Anderson et al.[21] (2008) Aliskiren 150 to 300 mg QD vs ramipril 5 to 10 mg QD The addition of HCTZ was allowed in patients not achieving adequate blood	AC, DB, MC, PC, RCT Men and women ≥18 years with essential hypertension (mean sitting DBP 90-109 mm Hg)	N=842 26 weeks	Primary: Change in mean sitting DBP at week 26 Secondary: Change in mean sitting SBP at week 26, change in mean sitting SBP and DBP at week 6 and 12 (comparing aliskiren and ramipril monotherapy), proportion	Primary: Reductions in mean sitting DBP at week 26 were significantly greater with aliskiren-based therapies (–13.2 mm Hg) than with ramipril-based therapies (–12.0 mm Hg; P=0.0250). Secondary: Reductions in mean sitting SBP at week 26 were significantly greater with aliskiren-based therapies (–17.9 mm Hg) than with ramipril-based therapies (–15.2 mm Hg; P=0.0036). Mean changes in sitting SBP were significantly greater with aliskiren (–12.9 and –14.0 mm Hg, respectively) than ramipril (–10.5 and –11.3, respectively) at weeks 6 and 12 (P=0.0041 and P=0.0027, respectively). Mean changes in sitting DBP were not significantly greater with aliskiren (–10.5 and –11.3 mm Hg, respectively) than ramipril (–9.5 and –9.7,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pressure control.			achieving blood pressure control (<140/90 mm Hg), proportion achieving SBP control (<140 mm Hg), safety	respectively) at week 6 but were significantly greater at week 12 (P=0.0689 and P=0.0056, respectively). The proportion of patients achieving overall blood pressure control <140/90 mm Hg was significantly higher with aliskiren-based therapy (61.4%) than with ramipril-based therapy (53.1%; P=0.0205) at week 26. Also, the proportion of patients achieving SBP control <140 mm Hg was significantly higher with aliskiren-based therapy (72.5%) than with ramipril-based therapy (64.1%; P=0.0075) at week 26. The majority of adverse events reported during the active treatment period were mild or moderate in intensity and transient. Most events occurred at a similar incidence in the 2 groups with the exception of cough which was considered treatment-related in 5.5% of patients receiving ramipril versus 2.1% of patients receiving aliskiren.
Oparil et al.[27] (2007) Aliskiren 150 to 300 mg QD vs valsartan 160 to 320 mg QD vs aliskiren 150 to 300 mg and valsartan 160 toe 320 mg QD (single entity products) vs	DB, MC, PC, RCT Men and women aged 18 years or over with stage 1-2 essential hypertension (mean sitting DBP 95-109 mm Hg and 8-hour ambulatory DBP ≥90 mm Hg)	N=1,797 8 weeks	Primary: Change in mean sitting DBP Secondary: Change in mean sitting SBP, proportion of patients achieving a successful response to treatment (mean sitting DBP <90 mm Hg and/or ≥10 mm Hg reduction from baseline) or achieving blood pressure control (mean sitting SBP/DBP <140/90 mm Hg), change in 24-hour ABPM,	Primary: The combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting DBP from baseline by 12.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (–9.0 mm Hg; P<0.0001), valsartan 320 mg (–9.7 mm Hg; P<0.0001) or with placebo (–4.1 mm Hg; P<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting DBP than did placebo at week 8 (all P<0.0001). Secondary: The combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting SBP from baseline by 17.2 mm Hg, significantly more than either monotherapy with aliskiren 300 mg (–13.0 mm Hg; P<0.0001), valsartan 320 mg (–12.8 mm Hg; P<0.0001) or with placebo (–4.6 mm Hg; P<0.0001). Monotherapy with aliskiren or valsartan provided significantly greater reductions in mean sitting SBP than did placebo at week 8 end point (all P<0.0001). The proportion of patients achieving a successful response to treatment at week 8 was significantly higher with the combination of aliskiren and valsartan (66%) than with aliskiren alone (53%; P=0.0003) or valsartan alone (55%; P=0.0010). All active treatments were associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			change in biomarkers, safety	significantly greater responder rates than placebo (30%; all P<0.0001). The proportion of patients achieving blood pressure control was significantly greater in the combination group (49%) than in the aliskiren (37%; P=0.0005) or valsartan (34%; P<0.0001) monotherapy groups. All active treatments were associated with significantly greater control rates than placebo (16%; all P<0.0001). The combination of aliskiren and valsartan was significantly more effective in lowering mean 24-hour ambulatory SBP and DBP than was either agent alone (all P<0.0001). The greater reductions in ambulatory blood pressure with aliskiren plus valsartan were maintained throughout the entire 24-hour dosing interval. Aliskiren plus valsartan (P<0.0001) and monotherapy with aliskiren (P<0.0001) or valsartan (P=0.0002) provided significant increases in plasma renin concentrations versus placebo. Increases in plasma renin concentrations were significantly greater for the combination than aliskiren (P=0.0014) or valsartan (P<0.0001) monotherapy. Valsartan monotherapy produced significantly greater increases in plasma renin activity than placebo (160% vs 18%; P=0.0003). By contrast, aliskiren alone significantly reduced plasma renin activity by 73% (P<0.0001 vs placebo), while the combination of aliskiren plus valsartan led to a reduction in plasma renin activity of 44% (P<0.0001 vs placebo). The combination of aliskiren and valsartan (–31%; P<0.0001) and valsartan monotherapy (–25%; P=0.0007) provided significantly greater reductions in plasma aldosterone concentration than did placebo (+7%), while aliskiren monotherapy had no significant effect (–5.9%; P=0.1059). Rates of adverse events and laboratory abnormalities were similar in all groups.
Pool et al.[28] (2007) Aliskiren 75 to 300	DB, MC, PC, PG, RCT Men and women	N=1,123 8 weeks	Primary: Change in mean sitting DBP	Primary: Aliskiren 300 mg significantly (P<0.0001) lowered mean sitting DBP compared with placebo. Reductions in mean sitting DBP for aliskiren 75 and 150 mg compared to placebo failed to reach statistical significance

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD vs valsartan 80 to 320 mg vs aliskiren 75 to 300 mg and valsartan 80 to 320 mg (single entity products) vs valsartan 160 mg and HCTZ 12.5 mg (fixed-dose combination) vs placebo	≥18 years with mild-to-moderate essential hypertension (mean sitting DBP ≥95 mm Hg after a 3- to 4-week single-blind placebo run-in period)		Secondary: Change in mean sitting SBP and safety	(P=0.052 and P=0.051, respectively). Secondary: Aliskiren 300 mg significantly (P<0.0001) lowered mean sitting SBP compared with placebo. A statistically significant linear dose relationship was observed for the effect of aliskiren (75 to 300 mg) on mean sitting DBP (P=0.0002) and mean sitting SBP (P=0.0005). The effects of aliskiren monotherapy on mean sitting DBP and SBP across the 75 to 300 mg dose range were similar to the effects of valsartan 80 to 320 mg. Coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone. Reductions in mean sitting DBP and SBP obtained with aliskiren 150 mg plus valsartan 160 mg and aliskiren 300 mg plus valsartan 320 mg were not significantly different from those observed with valsartan 160 mg plus HCTZ 12.5 mg. Responder rates were significantly greater than placebo for all 3 aliskiren monotherapy groups and for all aliskiren plus valsartan combinations. The proportion of responders with aliskiren 75 mg plus valsartan 80 mg was significantly greater than either component monotherapy (P<0.05). There was no significant difference between the proportion of responders to aliskiren 150 mg plus valsartan 160 mg or aliskiren 300 mg plus valsartan 320 mg compared with valsartan 160 mg plus HCTZ 12.5 mg. Control rates were higher with aliskiren 300 mg compared with placebo and with valsartan 160 mg plus HCTZ 12.5 mg compared with aliskiren 150 mg plus valsartan 160 mg, but there were no significant differences between aliskiren plus valsartan combinations and the respective monotherapies. Aliskiren and valsartan were generally well tolerated either as monotherapy or in combination. The overall incidence of adverse events and rate of discontinuations because of adverse events were similar to placebo in all active treatment groups.
Geiger et al.[35] (2009)	RCT, DB, AC	N=641	Primary: Change in diastolic	Primary: After 8 weeks of therapy, the aliskiren/valsartan/HCTZ group showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aliskiren 150 to 300 mg QD added to existing HCTZ therapy vs valsartan 160 to 320 mg QD added to existing HCTZ therapy vs aliskiren 150 to 300 mg and valsartan 160 to 320 mg QD added to existing HCTZ therapy (single entity products) vs HCTZ 25 mg QD	Patients ≥18 years of age with mild to moderate essential hypertension who were taking HCTZ for 4 weeks with a diastolic blood pressure ≥95 mm Hg	8 weeks	blood pressure (DBP) at week 8 Secondary: Change in systolic blood pressure (SBP) at week 8, change in DBP and SBP at week 4, proportion of patients achieving BP control (SBP/DBP <140/90 mm Hg), change in plasma renin activity (PRA) and plasma renin concentration (PRC)	significantly greater reductions in SBP and DBP compared with the other groups. The additional SBP and DBP reductions were 7 mm Hg and 5 mm Hg, respectively compared to aliskiren/HCTZ (P<0.0001), 3 mm Hg and 2 mm Hg compared to valsartan/HCTZ (P<0.01), and 15 mm Hg and 10 mm Hg compared to HCTZ monotherapy (P<0.001). Aliskiren/HCTZ and valsartan/HCTZ were more effective than HCTZ monotherapy. Valsartan/HCTZ was more effective than aliskiren/HCTZ. SBP and DBP were reduced by 15 mm Hg and 11 mm Hg, respectively in the aliskiren/HCTZ group. SBP and DBP were reduced by 18 mm Hg and 14 mm Hg, respectively in the valsartan/HCTZ group. Secondary: BP control rate was significantly higher with aliskiren/valsartan/HCTZ compared to aliskiren/HCTZ (40.9%, P<0.001), valsartan/HCTZ (48.7%, P<0.001), and HCTZ monotherapy (20.5%, P<0.001). At week 4, a significantly greater BP control rate was observed for the aliskiren/valsartan/HCTZ group at lower doses (150/160/25 mg) compared with the respective doses of the other groups: aliskiren/valsartan/HCTZ (300/320/25 mg) group (56%) compared with aliskiren/HCTZ (36.6%, P<0.05), valsartan/HCTZ (42.2%, P<0.05), and HCTZ monotherapy (19.9%, P<0.01). At week 8, PRC was unchanged in the HCTZ group, but was significantly increased in other groups. A significant decrease in PRA from baseline was observed in the aliskiren/HCTZ group (P<0.001) and a significant increase was observed in the valsartan/HCTZ (P<0.001). In the HCTZ and aliskiren/valsartan/HCTZ groups, there was no change in PRA (both P>0.75).
Dietz et al.[38] (2008) Aliskiren 150 to 300 mg QD vs	RCT, DB, MC Patients ≥18 years of age with hypertension (mean sitting diastolic blood	N=694 12 weeks	Primary: Changes in mean sitting systolic blood pressure (msSBP) and mean sitting diastolic blood pressure	Primary: Treatment with aliskiren/atenolol led to a significantly greater reduction in msSBP by 17.3 mm Hg compared to aliskiren monotherapy (difference –2.9 mm Hg; P=0.039) or atenolol monotherapy (difference –3.0 mm Hg; P=0.034). There was no difference between msSBP reductions with aliskiren and atenolol monotherapy (difference –0.1 mm Hg; P=0.954).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atenolol 50 to 100 mg QD vs aliskiren 150 to 300 mg and atenolol 50 to 100 mg QD	pressure ≥95 and <110 mm Hg)		(msDBP), rates of BP control (<140/90 mm Hg), pulse pressure and pulse rate, plasma renin concentration (PRC), and plasma renin activity (PRA)	Treatment with aliskiren/atenolol led to a significantly greater reduction in msDBP by 14.1 mm Hg compared to aliskiren alone (difference –2.9 mm Hg; P<0.001), but not atenolol alone (difference –0.5 mm Hg; P=0.545). Reductions in msDBP with atenolol were larger than those observed with aliskiren (difference 2.4 mm Hg; P=0.003). Rates of BP control were higher with aliskiren/atenolol (51.3%) compared to aliskiren monotherapy (36.1%, P<0.001) or atenolol monotherapy (42.2%, P=0.009). There was no significant difference in BP control rates between aliskiren and atenolol monotherapy (P=0.388). Mean pulse pressure was reduced by 3.0 mm Hg with aliskiren/atenolol and aliskiren monotherapy. Atenolol monotherapy did not affect pulse pressure. Aliskiren monotherapy did not affect pulse rate. Significant mean reductions in pulse rate of >10 bpm were observed with atenolol monotherapy and the aliskiren/atenolol combination (both P<0.001 vs aliskiren monotherapy). Aliskiren monotherapy increased PRC by 241% and aliskiren/atenolol increased PRC by 85% (P=0.010 vs aliskiren). Atenolol monotherapy decreased PRC by 24% (P<0.001 vs aliskiren and aliskiren/atenolol). Aliskiren, atenolol and aliskiren/atenolol reduced PRA by 65%, 52% and 61%, respectively.
Stanton et al.[30] (2010) Aliskiren 300 mg QD vs irbesartan, losartan, valsartan, ramipril, HCTZ, placebo	MA Adults with mild to moderate essential hypertension	N=4,877 (8 trials) 4 to 12 weeks	Primary: Paradoxical blood pressure rises, as well as the percentage of patients with SBP increases (>10 or >20 mm Hg) or DBP increases (>5 or >10 mm Hg) from baseline	Primary: There were no significant differences among the pooled aliskiren, irbesartan, losartan, valsartan, ramipril, and HCTZ groups in the incidence of SBP increases >10 mm Hg (P=0.30) and >20 mm Hg (P=0.28) or DBP increases >5 mm Hg (P=0.65) and >10 mm Hg (P=0.5). Increases in SBP and DBP occurred significantly more frequently in the pooled placebo group than the aliskiren group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Diabetes/Diabetic Nephropathy/Renal Dysfunction				
Persson et al.[31] (2009) Aliskiren 300 mg QD vs irbesartan 300 mg QD vs aliskiren 300 mg QD and irbesartan 300 mg QD vs placebo	DB, XO, RCT Adults with type 2 diabetes, hypertension and albuminuria	N=26 Four 2-month treatment periods	Primary: Albuminuria (urinary albumin excretion rate) Secondary: 24-hour blood pressure and glomerular filtration rate	Primary: Treatment with aliskiren led to a significant reduction in albuminuria by 48% compared with placebo (P<0.001). Treatment with irbesartan led to a significant reduction in albuminuria by 58% compared with placebo (P<0.001). There was no significant difference in albuminuria between aliskiren and irbesartan (P value not reported). The combination of aliskiren and irbesartan significantly reduced albuminuria by 71% compared to placebo (P<0.001), which was also significantly better than with monotherapy (P<0.001 for aliskiren and P=0.028 for irbesartan). Secondary: Systolic and diastolic 24-h blood pressure were reduced by 3 mm Hg and 4 mm Hg, respectively by aliskiren (P=NS and P=0.009, respectively), 12 mm Hg and 5 mm Hg, respectively by irbesartan (P<0.001 and P=0.002, respectively), and 10 mm Hg and 6 mm Hg, respectively with the combination (P=0.001 and P <0.001, respectively) compared to placebo. There was no significant change in 24-h blood pressure with irbesartan compared to combination therapy. Glomerular filtration rate was significantly reduced 4.6 ml/min/1.73 m^2 with aliskiren (P=0.037), 8.0 ml/min/1.73 m^2 with irbesartan (P<0.001), and 11.7 ml/min/1.73 m^2 with the combination (P<0.001) compared to placebo.
Parving et al.[26] (2008) AVOID Aliskiren 150 mg QD for 3 months, then 300 mg QD for 3 months vs placebo	DB, MC, PC, RCT Patients 18 to 85 years of age with hypertension, type 2 diabetes and nephropathy who were receiving losartan 100 mg QD plus additional antihypertensive therapy to achieve blood pressure goal	N=599 24 weeks	Primary: Reduction in albumin-to-creatinine ratio Secondary: Blood pressure and adverse events	Primary: After 24 weeks, aliskiren 300 mg reduced the mean urinary albumin-to-creatinine ratio by 20% compared to placebo (95% CI, 9 to 30; P<0.001). After 12 weeks, aliskiren 150 mg decreased the mean urinary albumin-to-creatinine ratio by 11% compared to placebo (95% CI, 2 to 20; P=0.02). Secondary: The mean blood pressure in the aliskiren group was 2/1 mm Hg lower than that in the placebo group (P=0.07 for systolic pressure, P=0.08 for diastolic pressure). A reduction of ≥50% in albuminuria was seen in 24.7% of the patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study medications were added to losartan 100 mg and other pre-existing antihypertensive treatments.	of <130/80 mm Hg			who received aliskiren as compared with 12.5% of those who received placebo (P<0.001). The total numbers of adverse and serious adverse events were similar in the groups.
Miscellaneous				
Solomon et al.[32] (2009) ALLAY Aliskiren 300 mg QD vs losartan 100 mg QD vs aliskiren 300 mg and losartan 100 mg QD	AC, RCT Adults with hypertension and increased left ventricular wall thickness	N=465 9 months	Primary: Change in left ventricular mass	Primary: There were reductions in left ventricular mass from baseline in all treatment groups, with 4.9-g/m^2 (5.4%), 4.8-g/m^2 (4.7%), and 5.8-g/m^2 (6.4%) reductions in the aliskiren, losartan, and combination arms, respectively (P<0.0001 for all treatment groups). The reduction in left ventricular mass in the combination group was not significantly different from that with losartan alone (P=0.52). The difference in left ventricular mass regression between the aliskiren and losartan arms was within the prespecified non-inferiority margin, suggesting that aliskiren was as effective as losartan in reducing left ventricular hypertrophy (P<0.0001 for non-inferiority).
McMurray et al.[42] (2008) ALOFT Aliskiren 150 mg QD vs	RCT, DB, MC, PC Patients ≥18 years of age with NYHA class II to IV heart failure, current or past history of hypertension, and plasma brain natriuretic peptide	N=302 3 months	Primary: N-terminal pro-BNP (NT-proBNP), BNP, aldosterone, signs and symptoms of heart failure echocardiographic measures of cardiac size and	Primary: Plasma NT-proBNP increased by 762 pg/mL with placebo and decreased by 244 pg/mL with aliskiren (P=0.0106). BNP decreased by a mean of 12.2 pg/mL in the placebo group and by 61.0 pg/mL in the aliskiren group (P=0.0160). Plasma aldosterone did not differ between groups. Urinary aldosterone decreased with aliskiren by 9.24 nmol/d and by 6.96 nmol/d with placebo (P=0.0150).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	(BNP) concentration >100 pg/mL who had been treated with an ACE inhibitor (or angiotensin receptor blocker) and β-blocker		ventricular function, blood pressure, heart rate variability, quality of life, neurohumoral and inflammatory biomarkers, and glycemic measures	Plasma renin activity decreased 5.71 $ng \cdot mL^{-1} \cdot h^{-1}$ with aliskiren compared with a decrease of 0.97 $ng \cdot mL^{-1} \cdot h^{-1}$ with placebo (P<0.0001). There was no difference between treatments for change in signs or symptoms of heart failure, echocardiographic measurements of wall thickness, chamber volumes, or LVEF. The mean decrease in seated systolic blood pressure was 1.7 mm Hg in the placebo group and 4.1 mm Hg in the aliskiren group (P=0.2257). The mean decrease in seated diastolic blood pressure was 0.2 mm Hg in the placebo group and 2.9 mm Hg in the aliskiren group (P=0.0599). The mean increase in seated heart rate was 0.2 bpm in the placebo group and 1.1 bpm in the aliskiren group (P=0.6774). Mean standing systolic blood pressure decreased by 1.7 mm Hg in the placebo group and by 3.5 mm Hg in the aliskiren group (P=0.497). The mean standing diastolic blood pressure increased by 0.7 mm Hg with placebo and decreased by 3.5 mm Hg with aliskiren (P=0.0045). The mean standing heart rate decreased by 0.3 bpm in the placebo group and increased by 0.7 bpm in the aliskiren group (P=0.466). There were no differences between treatments in any of the other prespecified comparisons, including autonomic measurements, the Kansas City Cardiomyopathy questionnaire, inflammatory and other plasma and urinary biomarkers (including urinary protein excretion), or measurements of glucose/insulin metabolism.

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, QD=once daily
Study abbreviations: AC=active-controlled, BMI=body mass index, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=cross-over
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, BMI=body mass index, DBP=diastolic blood pressure, SBP=systolic blood pressure

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 10. Relative Cost of the Renin Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Aliskiren	tablet	Tekturna®	$$$	N/A
Aliskiren and hydrochlorothiazide	tablet	Tekturna HCT®	$$$-$$$$	N/A
Aliskiren and valsartan	tablet	Valturna®	$$$	N/A

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

X. Conclusions

Aliskiren is the only renin inhibitor in this class and it is approved for the treatment of hypertension.[1-6] It is available as a single entity product, as well as in combination with hydrochlorothiazide or valsartan. There are no generic products currently available.

There are numerous national and international guidelines available that recommend the use of the ACE inhibitors or angiotensin II receptor antagonists in patients with acute coronary syndromes, cerebrovascular disease, coronary artery disease, diabetes, diabetic nephropathy, heart failure, hypertension, left ventricular dysfunction, left ventricular hypertrophy, previous myocardial infarction and renal disease. Aliskiren was approved by the FDA in 2007, and the fixed-dose combination products were subsequently approved in 2008 (Tekturna HCT®) and 2009 (Valturna®). Therefore, the guidelines do not provide specific recommendations regarding the use of

these agents.[10-16,33] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[10-11,13,16] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[12,33] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[12,33] All of the available guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[10-16,33] Most patients will need more than one antihypertensive medication to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[12,33] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

Several clinical trials have shown that aliskiren, aliskiren/hydrochlorothiazide, and aliskiren/valsartan effectively lower blood pressure.[17-25,27-29,31,35-41] The reduction in blood pressure with aliskiren monotherapy was similar to monotherapy with ACE inhibitors, angiotensin II receptor blockers, β-blockers and dihydropyridines.[20,23-25,27-28,38,41] In clinical trials comparing combination therapy to monotherapy, the more aggressive treatment regimen lowered blood pressure to a greater extent than the less-intensive treatment regimen.[19-20,27-28,35,37,39,41] Aliskiren has been shown to have positive effects on surrogate markers of cardiovascular and renal damage in patients with type 2 diabetes and nephropathy, heart failure and left ventricular hypertrophy.[26,31-32,42] However, the effects of aliskiren on hard cardiovascular and renal endpoints have not been established. There are several outcomes trials currently underway with aliskiren.

At this time, there is insufficient evidence to conclude that the renin inhibitors offer a significant clinical advantage over other alternatives in general use. Therefore, all brand renin 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 renin 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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I. Overview

Diuretics are commonly used for the treatment of hypertension, heart failure and various edematous conditions.[1-2] These agents act at different sites within the nephron, which leads to the increased urinary excretion of sodium, chloride and water.[2] The diuretics are categorized into several different AHFS classes, including loop diuretics, potassium-sparing diuretics, thiazide diuretics, thiazide-like diuretics, vasopressin antagonists and miscellaneous diuretics. 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 loop diuretics are approved for the treatment of edema and hypertension.[1-10] They primarily act in the thick ascending limb of the loop of Henle to increase the urinary excretion of sodium, chloride and water.[4-9] Furosemide and ethacrynic acid also inhibit the absorption of sodium and chloride in the proximal and distal tubules.[7-9] Bumetanide may also have an additional action in the proximal tubule.[6] The loop diuretics are considered to be the most potent diuretics. When given at their maximum dosages, they can lead to the excretion of up to 20% to 25% of the filtered sodium.[2] As renal function declines (glomerular filtration rate <30 ml/minute), a loop diuretic should be considered rather than a thiazide diuretic.[1] Loop diuretics do not possess the added property of arterial vasodilation, as seen with the thiazide diuretics. Some studies have suggested that hydrochlorothiazide (a thiazide diuretic) is more effective in lowering blood pressure than the loop diuretics.[10]

The loop diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Bumetanide, furosemide and torsemide are available in a generic formulation. This class was last reviewed in September 2008.

Table 1. Loop Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Bumetanide	injection, tablet	N/A	bumetanide
Ethacrynate sodium	injection^	Sodium Edecrin®	none
Ethacrynic acid	tablet	Edecrin®	none
Furosemide	injection, solution, tablet	Lasix®*	furosemide
Torsemide	injection, tablet	Demadex®*	torsemide

*Generic is available in at least one dosage form or strength.
^Product is primarily administered in an institution.
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 loop diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of heart failure and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Loop Diuretics

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases (AASLD): **Management of Adult Patients with Ascites Due to Cirrhosis: An Update[46] (2009)**	• First-line treatment of patients with cirrhosis and ascites consists of sodium restriction and diuretics (oral spironolactone with or without oral furosemide). • The typical diuretic regimen consists of single morning doses of spironolactone, beginning with 100 mg, in addition to furosemide 40 mg. Single morning dosing improves adherence.

Clinical Guideline	Recommendation(s)
	• Spironolactone monotherapy may be used only in patients who have minimal fluid overload. • In patients experiencing painful gynecomastia with spironolactone, amiloride may be an appropriate substitute. However, amiloride has been shown to be less effective than an active metabolite of spironolactone. • Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites. Hydrochlorothiazide can also cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses.
World Gastroenterology Organization (WGO) Practice Guideline: **Management of Ascites Complicating Cirrhosis in Adults**[47]	• Initial oral diuretic therapy consists of single daily doses of spironolactone or spironolactone in addition to furosemide. • Spironolactone monotherapy is more effective compared to furosemide monotherapy. However its use should be restricted to patients exhibiting minimal fluid overload. • Spironolactone monotherapy may be complicated by hyperkalemia and gynecomastia. Amiloride and triamterene are substitutes for spironolactone. • Indications of diuretic resistance include minimal to no weight loss and urinary sodium excretion of <78 mmol/day. Diuretic therapy should be discontinued in patients who develop encephalopathy, clinically significant complications of diuretics, hyperkalemia, metabolic acidosis with spironolactone, and whose serum sodium is <120 mmol/L or serum creatinine >2 mg/dL.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline**[20] **(2010)**	<u>Patients With Left Ventricular Systolic Dysfunction</u> • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • Torsemide may be considered in patients in whom erratic diuretic effect or absorption is present, particularly those with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • The addition of metolazone or chlorothiazide to loop diuretics should be considered in patients with persistent fluid retention despite high-dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion. • Patients requiring diuretic therapy to treat fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • Diuretic treatment is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate,

Clinical Guideline	Recommendation(s)
	treatment with a loop diuretic should be implemented. Patients With Acute Decompensated Heart Failure (ADHF) • It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally. • Intravenous vasodilators and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. Patients With Heart Failure and Hypertension • The use of an ACE inhibitor is recommended. • The addition of a β-blocker is recommended even if blood pressure is controlled. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine CCB (e.g., amlodipine or felodipine) or other antihypertensive drugs.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**[19] **(2009)**	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. Patients With Refractory End-Stage Heart Failure (Stage D) • Treatment of fluid retention is important. Hospitalized Patients • For patients admitted with heart failure who have evidence of significant fluid overload, intravenous loop diuretics should be started as soon as possible in the emergency department. If patients are already receiving loop diuretics, the initial intravenous dose should equal or exceed their chronic daily oral dose. • When diuresis is inadequate to relieve congestion, the diuretic regimen should be intensified using either a higher dose of loop diuretic, addition of a second diuretic, or continuous infusion of a loop diuretic.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[21] **(2008)**	Pharmacologic Therapy of Chronic Heart Failure • Diuretics are recommended in patients with heart failure and clinical signs or symptoms of congestion. • Diuretics cause activation of the renin–angiotensin–aldosterone system in patients with mild symptoms of heart failure and should usually be used in combination with an ACE inhibitor or ARB. • In general, a loop diuretic will be required in moderate or severe heart failure. A thiazide may be used in combination with loop diuretics for resistant edema, but with caution to avoid dehydration, hypovolemia, hyponatremia, or hypokalemia. Management of Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (HFPEF) • Diuretics are used to control sodium and water retention and relieve shortness of breath and edema.

Clinical Guideline	Recommendation(s)
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management[15] (2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[13] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics).
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[14] (2006)**	• If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.
National Heart, Lung, and Blood	• High-risk conditions with compelling indications for individual drug

Clinical Guideline	Recommendation(s)
Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[3] (2004)**	classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[18] (2004)**	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.
World Health Organization (WHO)/International Society of Hypertension (ISH): **WHO/ISH Statement on Management of Hypertension[12] (2003)**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans[17] (2003)**	• Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.

Clinical Guideline	Recommendation(s)
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[16] **(2010)**	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed, a thiazide diuretic may be added if estimated glomerular filtration rate (GFR) is ≥30 ml/min/1.73 m^2 or a loop diuretic for patients whose estimated GFR is <30 ml/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the loop diuretics 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 Loop Diuretics[4-9]

Indication	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Edema				
Treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome	✔	✔	✔	✔
Intravenous administration when a rapid onset of diuresis is desired (e.g., in acute pulmonary edema) or when gastrointestinal absorption is impaired or oral medication is not practical	✔	✔	✔	✔
Hypertension				
Treatment of hypertension			✔ *	✔ *
Miscellaneous				
Short-term management of ascites due to malignancy, idiopathic edema, and lymphedema		✔		
Short-term management of hospitalized pediatric patients, other than infants, with congenital heart disease or nephrotic syndrome		✔		

*Alone or in combination with other antihypertensive agents.

IV. Pharmacokinetics

The pharmacokinetic parameters of the loop diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Loop Diuretics[4-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Bumetanide	80-95	90-99	Liver, partial	Renal (50-81) Feces (10-20) Bile (2)	1-1.5
Ethacrynic acid	100	90	Liver	Renal (66)	1-4
Furosemide	47-70	91-99	Liver (10)	Renal (60-90) Feces (7-9)	0.5-2
Torsemide	80-90	99	Liver (80)	Renal (69)	3-6

V. Drug Interactions

Significant drug interactions with the loop diuretics are listed in Table 5.

Table 5. Significant Drug Interactions with the Loop Diuretics[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
Furosemide	1	Disulfiram	Inhibition of aldehyde dehydrogenase by disulfiram leads to the development of toxic intermediate metabolites. The combination of furosemide and disulfiram may produce acute alcohol intolerance.
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	1	Aminoglycosides	Auditory toxicity may be increased by possible synergistic activity. The mechanism is unknown.
Furosemide	2	Bile acid sequestrants	Bile acid sequestrants may bind to and impair oral absorption of furosemide when administered simultaneously. The diuretic effects of furosemide may be decreased by bile acid sequestrants.
Furosemide	2	Metronidazole and derivatives	Metronidazole and derivatives may inhibit aldehyde dehydrogenase-medicated metabolism of ethanol and cause a toxic accumulation of acetaldehyde. The combination of metronidazole/derivatives and furosemide may produce alcohol intolerance reactions.
Loop diuretics (bumetanide, ethacrynic acid, furosemide)	2	Chloral hydrate	The combination of bumetanide with chloral hydrate may produce unexpected diaphoresis, uneasiness, tachycardia and a variable change in blood pressure in certain patients. The mechanism is unknown.
Loop diuretics (bumetanide, ethacrynic acid, furosemide)	2	Ibuprofen and derivatives	Ibuprofen and derivatives may decrease natriuresis and diuresis of bumetanide by inhibiting the synthesis of renal prostaglandins. The diuretic effects may be decreased. Sodium retention and hypervolemia may occur.
Loop diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)	2	Lithium	Increased plasma lithium concentrations increase risk of toxicity. The mechanism is unknown.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the loop diuretics are listed in Table 6. The boxed warning for the loop diuretics is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Loop Diuretics[4-9]

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Cardiovascular				
Atrial Fibrillation	-	-	-	✔
Chest pain	<1	-	-	1
Edema	-	-	-	1
Electrocardiogram changes	<1	-	-	2
Hypotension	<1	-	✔	✔
Hypovolemia	-	✔	-	✔
Myalgia	-	-	-	2
Orthostatic hypotension	<1	-	✔	✔
Shunt thrombosis	-	-	-	✔
Syncope	-	-	-	✔
Ventricular tachycardia	-	-	-	✔
Central Nervous System				
Apprehension	-	✔	-	-
Asterixis	<1	-	-	-
Asthenia	-	-	✔	2
Confusion	-	✔	-	-
Dizziness	1	-	✔	3
Fatigue	<1	✔	-	✔
Headache	<1	✔	✔	7
Insomnia	-	-	-	1
Nervousness	-	-	-	1
Paresthesia	-	-	✔	-
Restlessness	-	-	✔	-
Vertigo	<1	✔	✔	-
Xanthopsia	-	-	✔	-
Dermatologic				
Erythema multiforme	-	-	✔	-
Exfoliative dermatitis	-	-	✔	-
Hives	<1	-	-	-
Itching	<1	-	-	-
Pruritus	<1	-	✔	✔
Rash	<1	✔	✔	✔
Photosensitivity	-	-	✔	-
Purpura	-	-	✔	-
Scaling eczema	-	-	✔	-
Stevens-Johnson Syndrome	-	-	✔	-
Urticaria	-	-	✔	-
Endocrine and Metabolic				
Acute gout	-	✔	-	✔
Dehydration	<1	-	-	-
Electrolyte imbalance	-	-	✔	✔
Nipple tenderness	<1	-	-	-
Gastrointestinal				
Abdominal discomfort/pain	<1	✔	-	-
Anorexia	-	✔	✔	-
Constipation	-	-	✔	2
Diarrhea	<1	✔	✔	2

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Dry mouth	<1	-	-	-
Dyspepsia	<1	-	✔	2
Dysphagia	-	✔	-	✔
Gastrointestinal bleed	-	✔	-	✔
Loss of appetite	-	-	✔	-
Malaise	-	✔	-	-
Nausea	<1	✔	✔	2
Pancreatitis	-	✔	✔	-
Polydipsia	-	-	-	✔
Vomiting	<1	✔	✔	✔
Genitourinary				
Difficulty maintaining an erection	<1	-	-	-
Premature ejaculation	<1	-	-	-
Hematologic				
Agranulocytosis	-	✔	✔	-
Anemia	-	-	✔	-
Aplastic anemia	-	-	✔	-
Deviations in differential counts	<1	-	-	-
Deviations in hematocrit	<1	-	-	-
Deviations in hemoglobin	<1	-	-	-
Deviations in prothrombin time	<1	-	-	-
Deviations in white blood cell count	<1	-	-	-
Hemolytic anemia	-	-	✔	-
Henoch-Schönlein purpura	-	✔	-	-
Leukopenia	-	-	✔	-
Neutropenia	-	✔	-	-
Thrombocytopenia	<1	✔	✔	-
Hepatic				
Abnormal liver enzymes	✔	✔	-	-
Encephalopathy	<1	-	-	-
Jaundice	-	✔	✔	-
Laboratory Test Abnormalities				
Azotemia	11	-	-	-
Changes in alkaline phosphatase	<1	-	-	-
Changes in cholesterol	<1	-	-	-
Changes in serum proteins	<1	-	-	-
Changes in total serum bilirubin	<1	-	-	-
Hyperlipidemia	✔	✔	✔	✔
Hyperglycemia	7	✔	✔	✔
Hyperuricemia	18	✔	✔	✔
Hypernatremia	<1			
Hypocalcemia	✔	✔	✔	✔
Hypochloremia	15	-	-	-
Hypoglycemia	-	✔	-	-
Hypokalemia	15	✔	✔	✔
Hypomagnesemia	✔	✔	✔	✔
Hyponatremia	9	-	-	-
Serum creatinine increased	7	-	-	-
Variations in bicarbonate	3	-	-	-
Variations in calcium	2	-	-	-
Variation in CO_2 content	4	-	-	-
Variations in phosphorus	5	-	-	-
Musculoskeletal				
Arthralgia	-	-	-	2

Adverse Events	Bumetanide	Ethacrynic Acid	Furosemide	Torsemide
Arthritic pain	<1	-	-	✔
Muscle cramps	1	-	✔	✔
Musculoskeletal pain	<1	-	-	-
Spasticity	-	-	✔	-
Renal				
Changes in creatinine clearance	<1	-	-	-
Glycosuria	<1	-	✔	-
Hematuria	-	✔	-	-
Interstitial nephritis	-	-	✔	-
Polyuria	-	-	-	7
Proteinuria	<1	-	-	-
Renal Failure	<1	-	-	-
Respiratory				
Cough	-	-	-	2
Hyperventilation	<1	-	-	-
Rhinitis	-	-	-	3
Special Senses				
Blurred vision	-	✔	✔	-
Deafness	-	✔	-	-
Ear discomfort	<1	-	-	-
Fullness of ears	-	✔	-	-
Impaired hearing	<1	✔	✔	-
Ototoxicity	✔	✔	✔	✔
Tinnitus	-	✔	✔	-
Other				
Angioedema	-	-	-	✔
Chills	-	✔	-	-
Fever	-	✔	✔	-
Necrotizing angitis	-	-	✔	-
Systemic vasculitis	-	-	✔	-
Sore Throat	-	-	-	2
Sweating	<1	-	-	-
Thrombophlebitis	-	-	✔	-
Weakness	<1	-	✔	✔

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for the Loop Diuretics (excluding torsemide)[4]

WARNING
Loop diuretics are potent diuretics which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dosage schedule have to be adjusted to the individual patient's needs.

VII. Dosing and Administration

The usual dosing regimens for the loop diuretics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Loop Diuretics[4-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Bumetanide	Edema: Injection: 0.5 to 1 mg over 1 minute; maximum, 10 mg/day Tablet: 0.5 to 2 mg/day; maximum, 10 mg/day	Safety and efficacy in children have not been established.	Injection: 0.25 mg/ml Tablet: 0.5 mg 1 mg 2 mg
Ethacrynic acid	Edema: 50 to 200 mg/day	Edema: Initial: 25 mg/kg; maximum, 3 mg/kg/day	Tablet: 25 mg
Furosemide	Acute Pulmonary Edema: Injection: 40 mg IV over 1 to 2 minutes; may increase to 80 mg IV Edema: Injection: 20 to 40 mg as a single IV/IM dose; may repeat in 2 hours or increased by 20 mg until desired response Oral: 20 to 80 mg/days; maximum, 600 mg/day Hypertension: Oral: 80 mg/day	Edema: Injection: initial, 1 mg/kg; may increase by 1 mg/kg not sooner than 2 hours after the previous dose; maximum, 6 mg/kg per dose Oral: 2 mg/kg as a single dose; maximum, 6 mg/kg per dose	Injection: 10 mg/ml Solution: 10 mg/ml 40 mg/4 ml 40 mg/5 ml Tablet: 20 mg 40 mg 80 mg
Torsemide	Chronic Renal Failure: 20 mg once daily; maximum, 200 mg Congestive Heart Failure: 10-20 mg once daily; maximum, 200 mg Hepatic Cirrhosis: 5-10 mg once daily; maximum, 40 mg Hypertension: 5 to 10 mg/day; maximum, 10 mg	Safety and efficacy in children have not been established.	Injection: 20 mg/2 ml 50 mg/5 ml Tablet: 5 mg 10 mg 20 mg 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the loop diuretics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Loop Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cirrhosis				
Laffi et al.[48] (1991) Furosemide 25 mg/day vs torasemide† 10 mg/day	RCT, DB Nonazotemic cirrhotic patients with ascites	N=24 3 days	Primary: Percent increase in natriuresis, body weight loss, percent increase in diuresis, plasma aldosterone concentration, plasma renin activity	Primary: Treatment with torasemide led to significantly greater natriuresis than furosemide (P<0.02). There was a greater percentage increase in basal values (day 1: 130% vs 50%; day 2: 104% vs 42%; and day 3: 65% vs 26%, respectively). Body weight loss was significantly higher with torasemide (2.5 kg) than with furosemide (1.3 kg; P<0.02). There was no significant difference (P=0.08) in the percent increase in diuresis among the treatment groups (day 1: 60% vs 26%; day 2: 35% vs 27%; day 3: 31% vs 24%). Plasma aldosterone concentrations (ng/ml) with torasemide were 0.79 and 0.94 at baseline and day 3, respectively. Plasma aldosterone concentrations with furosemide were 0.54 and 0.52 at baseline and day 3, respectively. Plasma renin activity (ng/ml/h) with torasemide were 5.8 and 9.4 at baseline and day 3, respectively. Plasma renin activity with furosemide were 4.2 and 5.4 at baseline and day 3, respectively.
Gerbes et al.[49] (1993) Furosemide 80 mg as a single dose vs torasemide† 20 mg as a single dose	RCT, DB, XO Patients with cirrhosis and ascites	N=28 24 hours	Primary: Urine volume, urine sodium volume, urine potassium volume, plasma aldosterone concentration, plasma renin activity	Primary: Treatment with torasemide led to greater cumulative 24 hour diuresis than furosemide (2863 vs 2111;P<0.05). There was no difference in cumulative 0–6 hour sodium excretion with torasemide or furosemide (95.7 vs 92.1 mmol, respectively; P=NS). There was greater cumulative 6–24 hour sodium excretion with torasemide compared to furosemide (38.4 vs 16.6 mmol; P<0.05). There was no difference in cumulative 0–24 hour sodium excretion with torasemide or furosemide (134.0 vs 108.5 mmol, respectively; P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in cumulative 0–6 hour potassium excretion with torasemide or furosemide (57.5 vs 39.9 mmol, respectively; P=NS). There was greater cumulative 6–24 hour potassium excretion with torasemide compared to furosemide (36.0 vs 27.6 mmol; P<0.05). There was no difference in cumulative 0–24 hour potassium excretion with torasemide or furosemide (88.3 vs 68.0 mmol, respectively; P=NS). Plasma aldosterone concentrations (ng/100 ml) with torasemide were 111.9 and 132 at baseline and 24 hours, respectively. Plasma aldosterone concentrations with furosemide were 105.7 and 131 at baseline and 24 hours, respectively. Plasma renin activity (ng/ml/h) with torasemide were 29.9 and 30.6 at baseline and 24 hours, respectively. Plasma renin activity with furosemide were 34.7 and 36.8 at baseline and 24 hours, respectively.
Fiaccadori et al.[50] (1993) Furosemide 50 mg/day vs torasemide 20 mg/day Patients also received spironolactone 200 mg/day	RCT, DB Nonazotemic cirrhotic patients with controlled ascites	N=28 10 weeks	Primary: Excretion of phosphate, free water, sodium, potassium, calcium, and uric acid	Primary: Furosemide produced more excretion of phosphates (P<0.001) and magnesium (P<0.05) compared to torasemide. Torasemide produced more excretion of free water (P<0.02). There was no difference in the excretion of sodium, potassium, calcium, or uric acid among the treatment groups.
Abecasis et al.[43] (2001) Frusemide* 40 mg/day	R, OL Cirrhotic patients with ascites	N=46 11 to 12 days	Primary: Resolution of ascites, weight loss, diuretic dosage, diuretic response	Primary: There was no difference in the percentages of patients with resolution of ascites with torsemide compared to frusemide (73% vs 75%; P=NS). There was no difference in weight loss with torsemide compared to frusemide (8 vs 8.5 kg; P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs torsemide 20 mg/day Patients also received spironolactone 200 mg/day				More patients receiving frusemide required an increase in diuretic dosage (37.5%) than with torsemide (9%; P<0.05). Torsemide produced a greater diuretic response in 24 hours than frusemide (P<0.007).
Heart Failure/Edema				
Hutcheon et al.[25] (1981) Bumetanide 1 to 2 mg/day vs furosemide 80 mg/day	DB, PG Patients with severe edema associated with congestive heart failure	N=20 3 days	Primary: Edema, symptoms of heart failure, safety and tolerability	Primary: Each agent was effective in decreasing the edema and relieving the symptoms of heart failure. Side effects were not severe and were similar in both treatment groups. Muscle cramps and abdominal pain were deemed not severe. Electrolyte shifts indicative of hypochloremic alkalosis and hyponatremia were seen in two patients in the bumetanide group.
Konecke et al.[26] (1981) Bumetanide vs furosemide No dose or frequency reported.	OL, PG, RCT Men and women with clinically detectable edema and signs and symptoms of congestive heart failure (e.g., rales, gallop rhythm, orthopnea, dyspnea, engorged neck veins, paroxysmal nocturnal dyspnea, congested liver, etc.)	N=42 6 months	Primary: Changes in weight, blood pressure, pulse, signs and symptoms of congested heart failure, electrolytes and functional capacity, safety and tolerability	Primary: There were no statistical differences in changes in body weight, blood pressure, edema, abdominal girth, and hepatomegaly and other signs and symptoms of congestive heart failure in patients receiving bumetanide vs furosemide. There were variable minor changes in serum sodium, potassium, chloride, and uric acid in both groups throughout the treatment. Changes remained within normal limits and reached significance for chloride at weeks 8 and 16 in the bumetanide group. Functional capacity improved slightly or remained unchanged throughout treatment in both treatment groups. There were no major side effects that were medication related in both treatment groups.
Nicholson et al.[27]	RCT, XO	N=10	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1977) Bumetanide 1 mg/day alternating with 3 mg/day for 3 months vs frusemide* 40 mg/day alternating with 160 mg/day for 3 months	Patients with cirrhosis and fluid overload	6 months	Ascites and edema Secondary: Adverse events	Bumetanide and frusemide were both effective in controlling ascites and edema, with 9 out of 10 patients showing a satisfactory response. Secondary: Side effects were reported in 6 patients. The most common side effects were urinary frequency and nocturia, which occurred in 4 patients taking bumetanide and 1 patient taking frusemide. There was 1 patient on bumetanide and 1 patient on frusemide who developed symptoms of postural hypotension.
Austin et al.[28] (1976) Ethacrynic acid 25 to 50 mg infused through a pulmonary artery catheter vs furosemide 40 to 60 mg infused through a pulmonary artery catheter	OS Men and women who underwent diagnostic right and transeptal left heart catheterization with chronic postcapillary pulmonary hypertension with heart failure NYHA Class II-IV	N=27 1 hour	Primary: Hemodynamic response (in the control state and at 20, 40, and 60 minutes after diuretic administration) including cardiac index, pulmonary artery, left atrial and systemic artery mean pressures, plasma volume, PBV and PEV	Primary: The hemodynamic response with each medication was similar. When compared to control state, the reductions in pulmonary artery mean pressure at 20, 40, and 60 minutes after diuretic infusion with either ethacrynic acid or furosemide were significant (P<0.001). The average left atrial mean pressure also decreased from 22 mm Hg during the control period to 18 mm Hg at 20 minutes and to 15 mm Hg at 60 minutes post diuretic infusion (ethacrynic acid or furosemide; P<0.001). The mean cardiac index decreased significantly at 20, 40, and 60 minutes compared to the control state after diuretic infusion with either ethacrynic acid or furosemide (P<0.001). There was a significant decrease in plasma volume at 60 minutes post drug infusions (ethacrynic acid or furosemide; P<0.001). In contrast, there was no significant change in PBV, PEV, PEV/PBV, and systemic arterial pressure throughout the study period with ethacrynic acid or furosemide.
Eshaghian et al.[23] (2006)	Cohort study, SC Men and women	N=1,354 2 years	Primary: All-cause mortality	Primary: There were 269 deaths during the 2-year follow-up, with 182 deaths by year 1 and 87 deaths during year 2. Of the 269 deaths, 91 deaths were due

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Furosemide 0 to 40 mg daily (group 1) vs furosemide 41 to 80 mg daily (group 2) vs furosemide 81 to 160 mg daily (group 3) vs furosemide >160 mg daily (group 4)	with advanced systolic heart failure referred to a single university medical center for heart failure management and/or transplant evaluation from 1985 to 2004		Secondary: Composite endpoint of death or urgent transplant	to progressive heart failure, 72 deaths were sudden, 8 deaths were secondary to myocardial infarction and 101 were unknown. Survival estimates at 1 year were 91%, 88%, 80%, and 69% for groups 1, 2, 3, and 4, respectively (P<0.0001). Survival estimates at 2 years were 83%, 81%, 68% and 53%, respectively (P<0.0001). Secondary: There were a total of 431 patients who received heart transplants by the end of the 2-year follow-up: 223 urgent and 208 elective. The hazard ratios for death from any cause, death and urgent transplantation, death from progressive heart failure, and sudden death for group 4 compared with group 1 were similar. On univariate analysis, compared with group 1, increasing loop diuretic dose were associated with a progressive increase in mortality (group 2: HR, 1.2; 95% CI, 0.8 to 1.7, group 3: HR, 2.1; 95% CI, 1.5 to 2.9, and group 4: HR, 3.4; 95% CI, 2.4 to 4.7).
Murray et al.[44] (2001) Furosemide vs torsemide	R, OL Patients with chronic heart failure	N=234 12 months	Primary: Readmission to the hospital for heart failure Secondary: Readmission for all cardiovascular causes and for all causes, numbers of hospital days, and health-related quality of life	Primary: Patients receiving torsemide were less likely to need readmission for heart failure (32%) compared to furosemide (17%; P<0.01). Secondary: Patients receiving torsemide were less likely to need readmission for all cardiovascular causes (59%) compared to furosemide (44%; P=0.03). There was no difference in the rate of admissions for all causes among the treatment groups (76% vs 71%; P=0.36). Patients treated with torsemide had significantly fewer hospital days for heart failure (106 vs 296 days; P=0.02). Improvements in fatigue scores from baseline were significantly greater among patients treated with torsemide compared to furosemide at months 2, 8, and 12 (P<0.05).
Cosín et al.[45]	OL	N=1,377	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Furosemide 40 mg/day orally or other diuretics vs torasemide† 10 mg/day orally	Patients with NYHA functional class II to III heart failure	12 months	Mortality, morbidity, functional class and serum potassium levels (<3.5 or >5 mEq/L)	Total mortality was significantly lower in the torasemide group (2.2%) compared to the furosemide/other diuretics group (4.5%; P<0.05). Cardiac mortality was lower in patients receiving torasemide (1.4%) than in those receiving furosemide/other diuretics (3.5%; P<0.05). NYHA improvement in at least 1 class occurred in more patients who received torasemide (45.8%) than those who received furosemide/other diuretics (37.2%; P=0.00017). Abnormal potassium levels were observed in fewer torasemide patients (12.9%) than furosemide/other diuretics patients (17.9%; P=0.013).
Muller et al.[29] (2003) Furosemide vs torasemide†	R, OL Patients with NYHA functional class II-IV congestive heart failure	N=237 9 months	Primary: Clinical improvement in heart failure, quality of life, hospitalizations, safety and tolerability	Primary: Clinical improvement in chronic heart failure was seen in both groups, but the trend to improve by at least one NYHA class was significant with torasemide (P=0.014) compared to furosemide-treated patients. There were no differences in adverse reactions and hospitalizations due to congestive heart failure.
Kasama et al.[30] (2006) Furosemide 20 to 40 mg/day vs torasemide† 4 to 8 mg/day	RCT Patients with non-ischemic congestive heart failure (left ventricular ejection fraction <45%) also being treated with an angiotensin converting enzyme inhibitor	N=40 6 months	Primary: Effect on cardiac sympathetic nerve activity (delayed heart to mediastinum count ratio, delayed total defect score, washout rate) Secondary: Effect on left ventricular remodeling (left ventricular end diastolic volume, left ventricular end	Primary: In the furosemide group at the end of treatment, mean heart to mediastinum count ratio increased from 1.68±0.18 to 1.71±0.19 (P=NS), mean total defect score decreased from 42±11 to 40±12 (P=NS), and mean washout rate decreased from 50±8% to 47±12% (P=NS). In the torasemide group at the end of treatment, mean heart to mediastinum count ratio increased from 1.61±0.19 to 1.77±0.24 (P<0.001), mean total defect score decreased from 44±8 to 36±8 (P<0.001), and mean washout rate decreased from 52±12% to 41±14% (P=0.001). Secondary: In the furosemide group left ventricular end diastolic volume decreased from 174±24 mL to 165±34 mL (P=NS), left ventricular end systolic volume decreased from 120±15 mL to 109±33 mL (P=NS), and left

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			systolic volume)	ventricular ejection fraction increased from 31±7% to 32±7% (P=NS). In the torasemide group left ventricular end diastolic volume decreased from 173±22 mL to 147±30 mL (P<0.01), left ventricular end systolic volume decreased from 117±19 mL to 95±25 mL (P<0.001), and left ventricular ejection fraction increased from 31±7% to 34±7% (P=NS).
Patterson et al.[24] (1994) Torsemide 5 mg QD vs torsemide 10 mg QD vs torsemide 20 mg QD vs placebo QD	DB, PC, MC, PG Men and women diagnosed with NYHA class II or III congestive heart failure and edema	N=66 7 days	Primary: Change in body weight from baseline Secondary: Change in urinary sodium, potassium, chloride excretion and urine volume after the first dose of drug	Primary: Patients receiving torsemide 10 and 20 mg had a significant decrease in weight (-1.62 and -1.30 kg, respectively) as compared to placebo. Torsemide 5 mg did not demonstrated a significant reduction in body weight compared to placebo (-0.60 kg). Secondary: Severity of edema decreased as the dose of torsemide increased. The adverse events did not increase with higher doses of torsemide.
Senzaki et al.[31] (2008) Torasemide† (de novo group) vs torasemide† (replacement group) was converted from	RCT Pediatric patients (age range from 3 weeks to 17 years) with congested heart failure, patients newly diagnosed with congestive heart failure or previously treated with	N=102 3-4 weeks	Primary: Clinical signs and symptoms of congestive heart failure Secondary: Humoral factors, serum potassium levels, and adverse events	Primary The de novo torasemide group significantly improved the congestive heart failure index from 7.2±1.6 to 5.7±1.4 (P<0.05); however the replacement group did not. The replacement group baseline value of the congestive heart failure index was 7.4±2.4 and after treatment the mean value was 6.8±2.3. Secondary: The de novo and replacement groups significantly improved brain natriuretic peptide and aldosterone levels (P<0.05); however, plasma rennin activity was not significantly decreased among both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
furosemide dosage using 0.2 mg torasemide corresponding to 1 mg furosemide	furosemide			Serum potassium levels were significantly increased in the replacement group (P<0.05), but not in the de novo group. The most commonly reported adverse events of torasemide were those associated with loop diuretics in general.
Faris et al.[22] (2006) Loop diuretics (furosemide, bumetanide), thiazide diuretics (chlorothiazide), or potassium-sparing diuretics (amiloride, triamterene) vs placebo or active control (ACE inhibitors, digoxin)	MA Adult patients with chronic heart failure	N=525 (14 trials) 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Mortality was reported in 3 of the 7 placebo-controlled trials, and this analysis showed that mortality was lower for patients treated with diuretics than with placebo (3/111[2.7%] vs 12/110 [10.9%], respectively; OR 0.24; 95% CI, 0.07 to 0.83; P=0.02). These results showed that patients treated with diuretics had an absolute risk reduction of 8% when compared to placebo and a number needed to treat of 12.5. Secondary: An analysis of pooled data from 2 trials showed lower admission rates for worsening heart failure in patients taking diuretics than in patients taking placebo (OR 0.07; 95% CI, 0.01 to 0.52; P=0.01). Diuretics were found to improve exercise capacity, with a difference in means of 0.74 (95% CI, 0.37 to 1.11; P<0.0001) and of 0.67 (95% CI, 0.02 to 1.31; P=0.04.), respectively. The combined results of these 4 trials indicated that diuretics improved exercise capacity in participants with chronic heart failure with a difference in means of 0.72 (95% CI, 0.40 to 14; P<0.0001).
Hypertension				
Van der Heijden et al.[34] (1998) Bumetanide 1 mg daily for 6 weeks vs	DB, PC, XO Patients with hypertension	N=27 24 weeks	Primary: Changes in blood pressure, serum lipid levels, lab values and safety and tolerability	Primary: Bumetanide and furosemide reduced SBP by 8.2% (P<0.0002) and DBP by 4.5% (P<0.002). Overall SBP and DBP measurements were 12 mm Hg and 4 mm Hg lower, respectively, when receiving bumetanide or furosemide vs placebo. Both furosemide and bumetanide increased total cholesterol by 5.0% (P<0.002), high-density lipoprotein cholesterol by 1.7% (P=NS), low-density lipoprotein cholesterol by 4.8% (P<0.01) and triglycerides by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
furosemide 40 mg daily for 6 weeks				12.4% (P<0.01). Serum glucose, magnesium, sodium and potassium levels were unchanged in both treatment groups; whereas serum creatinine tended to increase (3.2%; P=0.09). Side effects were mild in severity with no discontinuation reported. In both bumetanide and furosemide treated patients, four patients reported hypertonic muscles, but was resolved within a couple of days.
De Berrazueta et al.[32] (2007) Furosemide infused in 3 progressive solutions containing 475, 950, and 1,900 nmol/mL for arterial studies and 240, 480, and 960 nmol/mL for venous studies vs torasemide[†] infused in 3 solutions containing 400, 800, and 1,600 nmol/mL for arterial studies and 200, 400, and 800 nmol/mL for venous studies.	RCT Patients with hypertension and healthy controls	N=59 Single dose	Primary: Dilatory effect on arteries and veins	Primary: There were no significant changes in arterial dilation. Furosemide increased vasodilatation from 0.56±0.09 to 0.88±0.06 (P=0.000) in healthy control subjects and from 0.49±0.10 to 0.75±0.12 (P=0.000) in hypertensive patients. Torsemide increased venodilation from 0.46±0.06 to 0.70±0.11 (P=0.007) in control subjects and from 0.48±0.09 to 0.67±0.12 (P=0.03) in hypertensive patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Von Dossow et al.[33] (2008) Furosemide 40 mg IV and 80 mg PO 2 hours after extubation on day 1 after surgery vs torasemide[†] 20 mg IV and 20 mg PO 2 hours after extubation on day 1 after surgery	DB, RCT Patients with secondary pulmonary hypertension scheduled for elective valve replacement and/or coronary artery bypass graft	N=21 Day 1 after surgery	Primary: Cardiac output Secondary: Endothelin-1 and angiotensin-II	Primary: Cardiac output increased significantly (P=0.03) in the torasemide group compared to the furosemide group. Secondary: Endothelin-1 and angiotensin-II increased significantly (P=0.031) in the furosemide group compared to the torasemide group.
Vasavada et al.[35] (2003) <u>Phase 1: Inpatient</u> Furosemide 200 mg daily with sodium-free water (10 mL/kg) vs torsemide 100 mg daily with sodium-free water (10 mL/kg) <u>Phase 2:Outpatient</u> Furosemide 80 mg daily	DB, RCT, two-phase, XO Patients ≥18 years of age with chronic kidney disease (serum creatinine >1.4 mg/dL) and volume overload	N=14 3 weeks	Primary: <u>Phase 1: Inpatient</u> Change in 24-hour urinary sodium excretion <u>Phase 2: Outpatient</u> Primary: 24-hour ambulatory SBP Secondary: Potassium, calcium, protein excretion, diurnal variation of electrolyte and protein excretion, and glomerular filtration rate	Primary <u>Phase 1: Inpatient</u> Furosemide and torsemide increased urinary sodium excretion from 199 mEq/day to 357 mEq/day and 213 mEq/day to 398 mEq/day, respectively. These differences between the two diuretics were not statistically significant. <u>Phase 2: Outpatient</u> Both treatments had similar effects in reducing SBP (P=0.43). The SBP was reduced from baseline to post treatment by 9.7 mm Hg for torsemide (P=0.007) and 9.2 mm Hg for furosemide (P=0.021). Secondary: There were no significant differences in excretion rate profiles between torsemide and furosemide (P>0.17).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs torsemide 40 mg daily				
Pupita et al.[37] (1983) Furosemide 25 mg QD vs chlorthalidone 50 mg QD	RCT, XO Men and women with a mean age of 53.9±9.2 years with mild to moderate hypertension	N=36 12 months	Primary: Blood pressure Secondary: Plasma electrolytes, adverse events	Primary: Patients taking chlorthalidone had significantly lower SBP at each monthly measurement compared to baseline (P<0.01). However, only DBP values at month 5 were significant compared to baseline (P<0.05). Patients taking furosemide had significantly lower SBP at months 3, 4, and 5 compared to baseline (P<0.05 for month 3, and P<0.01 for months 4 and 5). DBP values were significantly lower at all monthly measurements compared to baseline in patients taking furosemide (P<0.01). At month 1, SBP decreased by 19.4 mm Hg with chlorthalidone and by 21.2 mm Hg with furosemide (P<0.001). DBP decreased by 11 mm Hg with chlorthalidone and by 12.6 mm Hg with furosemide at month 1 (P<0.001). Secondary: There were no significant changes in serum sodium levels with either chlorthalidone or furosemide. Patients taking chlorthalidone had significantly lower serum chloride levels compared to baseline at all points (P<0.01), whereas patients taking furosemide had significantly lower levels only at month 6 (P<0.05). Both chlorthalidone and furosemide significantly reduced serum potassium levels at all points compared to baseline (P<0.01). Patient taking chlorthalidone reported adverse effects including dizziness, transient abdominal disorder, and slight weakness. Patients taking furosemide reported transient early weakness and irritability. The rate of adverse events was not statistically significant in either treatment group.
Valmin K et al.[36] (1975) Furosemide 12.5, 25 or 40 mg BID	DB, RCT, XO, 5 experimental periods each of 4 weeks	N=34 20 weeks	Primary: Blood pressure, urinary output, serum electrolytes, safety and	Primary: When compared to placebo, there was a significant reduction of blood pressure with HCTZ 12.5 mg twice daily and furosemide 12.5 mg twice daily (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs HCTZ 12.5 mg BID vs placebo	Men and women with essential hypertension		tolerability	Paired comparison showed that HCTZ 12.5 mg twice daily and furosemide 25 and 40 mg twice daily had a similar hypotensive effect, irrespective of the initial blood pressure (P>0.10). When compared to placebo, the urinary output increased significantly with furosemide 12.5, 25, or 40 mg twice daily (P<0.05, P<0.01 and P<0.001, respectively) but not with the HCTZ group (P>0.10). Sodium level did not alter during the various treatment periods when compared with the placebo period, or between the individual treatment periods (P>0.10). Potassium level fell significantly during the HCTZ period (P<0.001) and furosemide 25 mg and 40 mg twice daily period (P<0.01 and P<0.001, respectively). Potassium level was not significantly affected with furosemide 12.5 mg twice daily (P>0.10).
Araoye et al.[38] (1978) Furosemide 40 mg BID vs HCTZ 50 mg BID	DB, XO Patients with hypertension	N=not specified 3 months	Primary: Blood Pressure	Primary: Furosemide and HCTZ significantly reduced blood pressure. The decrease in blood pressure was consistently greater in the HCTZ group than with furosemide; however the difference was significant in regards to SBP only.
Miscellaneous				
Bagshaw et al.[39] (2007) Loop diuretics (frusemide*, torasemide†) vs placebo	MA Patients with acute renal failure	N=555 Variable duration	Primary: Mortality, need for renal replacement therapy, and renal recovery Secondary: Urine output, serum potassium level and acid-base status, duration of	Primary: There was no statistical difference in mortality between loop diuretics compared to placebo (OR 1.28; 95% CI, 0.89 to 1.84; P=0.18). There was no statistical difference in renal recovery between loop diuretics and control (OR 0.88; 95% CI, 0.59 to 1.31; P=0.5). Secondary: Loop diuretics were associated with a shorter duration of renal replacement therapy (weighted mean difference of 1.4 days; 95% CI, 0.2 to 2.3; P=0.02), shorter time to spontaneous decline in serum creatinine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			acute renal failure or renal replacement therapy, length of hospital stay, and toxicity	level (weighted mean difference, 2.1 days; 95% CI, 0.4 to 3.7; P=0.01), and a greater increase in urine output from baseline (OR 2.6; 95% CI, 1.4 to 4.9; P=0.004). There was no data available on acid-base status, hospital status, hospital length of stay or health costs.
Galloe et al.[40] (2006) Bumetanide 0.5 mg (0, 1, 2, or 4 tablets twice daily) vs trandolapril 0.5 mg (0, 1, 2, or 4 tablets once daily)	DB, PC, RCT, XO Men and women with previous myocardial infarction at least 3 years ago, had medical treatment for heart failure and ejection fraction between 0.36 and 0.54 estimated by echo-cardiography (wall motion index)	N=16 14 days	Primary: Patient reported quality of life Secondary: Effects on the involved organs: kidney function, left ventricular function and blood pressure	Primary: Patient's well-being increased 12% with 0.5 mg bumetanide twice daily but higher doses bumetanide decreased patient's well-being by 12% compared to placebo (P<0.002). Increasing doses of bumetanide tended to increase tiredness (P=0.072). There were no statistically significant effects of bumetanide on the patient's opinion of their health, degree of dyspnea, appetite or work capacity. Secondary: Bumetanide increased 24-hour urine production in a straight dose-dependent manner (P<0.0001) while trandolapril had no effect (P=0.53). Bumetanide and trandolapril did not alter the 24-hour creatinine excretion and creatinine clearance (P=0.33, P=0.11 and P=0.53, P=0.97, respectively). Bumetanide decreased left ventricular function and increased heart rate in a dose dependent manner (P<0.001). Left ventricular function was also decreased with trandolapril but did not reach statistically significant. (P>0.062). Trandolapril significantly reduced SBP by maximally of 7.6 mm Hg (5.8%) with the lowest dose of 0.5 mg daily (P=0.007). Bumetanide had no significant effect on DBP (P=0.23).

*Synonym for furosemide.
† Synonym for torsemide.
Drug regimen abbreviations: BID=twice daily, IV, intravenous, PO=by mouth, QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, SC=single centre, SD=standard deviation, XO=crossover
Other abbreviations: DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, NYHA=New York Heart Association, PBV=pulmonary blood volume, PEV=pulmonary extravascular fluid volume, SBP=systolic blood pressure

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 10. Relative Cost of the Loop Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Bumetanide	injection, tablet	N/A	N/A	$
Ethacrynic acid	tablet	Edecrin®	$$$$$	N/A
Furosemide	injection, solution, tablet	Lasix®*	$	$
Torsemide	injection, tablet	Demadex®*	$-$$$$	$-$$$

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

X. Conclusions

All of the loop diuretics are approved for the treatment of edema associated with congestive heart failure, hepatic disease or renal disease.[4-10] Furosemide and torsemide are also approved for the treatment of hypertension. Additionally, ethacrynic acid is approved for the short-term treatment of ascites (due to malignancy, idiopathic edema, and lymphedema) and for the short-term treatment of hospitalized pediatric patients with congenital heart disease or the nephrotic syndrome. Bumetanide, furosemide and torsemide are available in a generic formulation.

Guidelines recommend the use of diuretics and sodium restriction for the management of ascites due to cirrhosis.[46-47] Spironolactone is recommended as first-line therapy, either as monotherapy or in combination with furosemide. Amiloride is an alternative treatment option in patients experiencing gynecomastia with

spironolactone. Triamterene, metolazone and hydrochlorothiazide have also been used to treat ascites. Several studies have compared furosemide and torsemide in cirrhotic patients with ascites.[43,48-50] Although torsemide significantly increased natriuresis and diuresis compared to furosemide, these effects were not consistently demonstrated across the studies. There was no difference in plasma renin or aldosterone concentrations among the treatment groups.

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload.[19-21] The loop diuretics are generally recommended as initial therapy in patients with left ventricular dysfunction.[20-21] For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[19-20] There are relatively few studies that have directly compared the loop diuretics for the treatment of chronic heart failure. In open-label trials, torsemide decreased mortality, hospitalizations and improved NYHA functional class compared to treatment with furosemide.[29,44-45] However, due to limitations in the study designs, it is difficult to draw firm conclusions about the results of these studies. The most commonly used loop diuretic for the treatment of heart failure is furosemide; however, some patients may respond more favorably to other agents. Torsemide is better absorbed than furosemide and has a longer duration of action. It may be appropriate to use in patients exhibiting an erratic diuretic effect and in those with refractory fluid retention despite high doses of other loop diuretics.[20]

There are several national and international organizations that have published guidelines on the treatment of hypertension.[3,12-18] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[3,12,14,18] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[13,15] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[13,15] Guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[3,12-18] Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Some studies suggest that hydrochlorothiazide is more effective than a loop diuretic for lowering blood pressure.[11,38] However, a loop diuretic should be used when the glomerular filtration rate is <30 mL/min.[13,16,18]

Serious adverse events reported with the loop diuretics include electrolyte abnormalities, hypersensitivity reactions and ototoxicity.[4-11] Ethacrynic acid has a higher rate of ototoxicity than other loop diuretics and is less commonly used. Patients allergic to sulfonamides may also show hypersensitivity to bumetanide, furosemide and torsemide.[4-6] Ethacrynic acid is the only loop diuretic that is not a sulfonamide derivative and can be safely used in patients with a sulfonamide allergy.[8]

There is insufficient evidence to support that one brand loop diuretic 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 loop diuretics 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 loop diuretic 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 Potassium-Sparing Diuretics
AHFS Class 402816
November 10, 2010

I. Overview

The potassium-sparing diuretics are approved for the treatment of congestive heart failure, edema and hypertension.[1-6] They inhibit sodium-potassium ion exchange at the distal convoluted tubule, cortical collecting tubule and collecting duct.[1-8] This reduces both potassium and hydrogen secretion and their subsequent excretion. When used alone, amiloride has a weak diuretic and antihypertensive effect and increases the risk of hyperkalemia.[4] The potassium-sparing diuretics are generally used in combination with other diuretics to help restore normal serum potassium levels or to prevent the development of hypokalemia. Amiloride and triamterene are both available as a fixed-dose combination with hydrochlorothiazide. Hydrochlorothiazide inhibits the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride.

The potassium-sparing diuretics 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 September 2008.

Table 1. Potassium-Sparing Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amiloride	tablet	Midamor®*	amiloride
Amiloride and hydrochlorothiazide	tablet	N/A	amiloride and hydrochlorothiazide
Triamterene and hydrochlorothiazide	capsule, tablet	Dyazide®*, Maxzide®*	triamterene and hydrochlorothiazide

*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 potassium-sparing diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of heart failure and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Potassium-Sparing Diuretics

Clinical Guideline	Recommendation(s)
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline[12] (2010)**	Patients With Left Ventricular Systolic Dysfunction • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • Torsemide may be considered in patients in whom erratic diuretic effect or absorption is present, particularly those with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • The addition of metolazone or chlorothiazide to loop diuretics should be considered in patients with persistent fluid retention despite high-dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion.

Clinical Guideline	Recommendation(s)
	• Patients requiring diuretic therapy to treat fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who restrict dietary sodium intake. Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction • Diuretic treatment is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. Patients With Acute Decompensated Heart Failure (ADHF) • It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally. • Intravenous vasodilators and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. Patients With Heart Failure and Hypertension • The use of an ACE inhibitor is recommended. • The addition of a β-blocker is recommended even if blood pressure is controlled. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine CCB (e.g., amlodipine or felodipine) or other antihypertensive drugs.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults[11] (2009)**	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. Patients With Refractory End-Stage Heart Failure (Stage D) • Treatment of fluid retention is important. Hospitalized Patients • For patients admitted with heart failure who have evidence of significant fluid overload, intravenous loop diuretics should be started as soon as possible in the emergency department. If patients are already receiving loop diuretics, the initial intravenous dose should equal or exceed their chronic daily oral dose. • When diuresis is inadequate to relieve congestion, the diuretic regimen should be intensified using either a higher dose of loop diuretic, addition of a second diuretic, or continuous infusion of a loop diuretic.
European Society of Cardiology (ESC): **Guidelines for the**	Pharmacologic Therapy of Chronic Heart Failure • Diuretics are recommended in patients with heart failure and clinical

Clinical Guideline	Recommendation(s)
Diagnosis and Treatment of Acute and Chronic Heart Failure[13] (2008)	signs or symptoms of congestion. • Diuretics cause activation of the renin–angiotensin–aldosterone system in patients with mild symptoms of heart failure and should usually be used in combination with an ACE inhibitor or ARB. • In general, a loop diuretic will be required in moderate or severe heart failure. A thiazide may be used in combination with loop diuretics for resistant edema, but with caution to avoid dehydration, hypovolemia, hyponatremia, or hypokalemia. <u>Management of Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (HFPEF)</u> • Diuretics are used to control sodium and water retention and relieve shortness of breath and edema.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management[18] (2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[16] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African

Clinical Guideline	Recommendation(s)
	American patients (CCBs, diuretics). • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated. • CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[17] (2006)**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[14] (2004)**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to

Clinical Guideline	Recommendation(s)
	CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2-4 times higher in African American patients. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia. • Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should not be used in patients whose potassium levels are greater than 5.0 mEq/L.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[21] (2004)**	• All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals. • Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence. • Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension[15] (2003)**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients.

Clinical Guideline	Recommendation(s)
	• Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[20] **(2003)**	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[19] **(2010)**	• Multiple drug therapy is generally required to achieve blood pressure goals. • No specific recommendation is made concerning the potassium-sparing diuretics.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the potassium-sparing diuretics 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 Potassium-Sparing Diuretics[1-6]

Indication	Amiloride	Amiloride/ HCTZ	Triamterene/ HCTZ
Edema or Hypertension			
Adjunctive treatment with thiazide diuretics or other kaliuretic diuretic agents in congestive heart failure or hypertension to help restore normal serum potassium levels in patients who develop hypokalemia on the kaliuretic diuretic	✔ †		
Adjunctive treatment with thiazide diuretics or other kaliuretic diuretic agents in congestive heart failure or hypertension to prevent development of hypokalemia in patients who would be exposed to particular risk if hypokalemia were to develop	✔ †		
Treatment of hypertension or congestive heart failure in patients who develop hypokalemia when thiazides or other kaliuretic diuretics are used alone, or in whom maintenance of normal serum potassium levels is considered to be important		✔ *‡	
Treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone			✔ *‡
Treatment of hypertension or edema for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked			✔ *‡

*Alone or in combination with other antihypertensive agents.
‡This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.
†Amiloride should rarely be used alone. It has weak (compared with thiazides) diuretic and antihypertensive effects. Used as single agents, potassium sparing diuretics, including amiloride, result in an increased risk of hyperkalemia (approximately 10% with amiloride).Amiloride should be used alone only when persistent hypokalemia has been documented and only with careful titration of the dose and close monitoring of serum electrolytes.

IV. Pharmacokinetics

The pharmacokinetic parameters of the potassium-sparing diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Potassium-Sparing Diuretics[1-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amiloride	30-90	NS	Not metabolized	Renal (50) Feces (40-50)	6-9
Amiloride and hydrochlorothiazide	A: 30-90 H: 60-80	A: NS H: 40	Not metabolized	A: Renal (50) Feces (40-50) H: Renal (>60)	A: 6-9 H: 10-12
Triamterene and hydrochlorothiazide	T: 30-70 H: 60-80	T: 55-67 H: 40	T: Liver (80)	T: Renal (21) H: Renal (>60)	T: 1.5-2.5 H: 10-12

A=amiloride, H=hydrochlorothiazide, NS=not significant, T=triamterene

V. Drug Interactions

Significant drug interactions with the potassium-sparing diuretics are listed in Table 5.

Table 5. Significant Drug Interactions with the Potassium-Sparing Diuretics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Amiloride	1	ACE inhibitors	Hyperkalemia, possibly with cardiac arrhythmias or arrest may occur with the combination of amiloride and ACE inhibitors. Decreased aldosterone activity by ACE inhibitors may function synergistically with potassium conservation by amiloride to produce substantial hyperkalemia.
Amiloride	1	Angiotensin II receptor antagonists (ARBs)	The risk of hyperkalemia may be increased when amiloride is co-administered with ARBs. Decreased aldosterone activity by ARBs may function synergistically with potassium conservation by amiloride to produce substantial hyperkalemia.
Hydrochlorothiazide	1	Dofetilide	Thiazide diuretics increase potassium excretion. Hypokalemia may occur, increasing the risk of torsades de pointes.
Hydrochlorothiazide	1	Lithium	Thiazide diuretics decrease the renal clearance of lithium which leads to increased serum lithium levels. Lithium toxicity has occurred.
Potassium-sparing diuretics (amiloride,	1	Aldosterone blockers	Aldosterone blockers and potassium-sparing diuretics may

Generic Name(s)	Significance Level	Interaction	Mechanism
triamterene)			exert additive pharmacologic effects. Hyperkalemia with the potential for cardiac arrhythmias may result.
Potassium-sparing diuretics (amiloride, triamterene)	1	Potassium preparations	Use of potassium preparations and potassium-sparing diuretics may increase the risk of hyperkalemia. Cardiac arrhythmias or cardiac arrest may occur.
Amiloride	2	Aliskiren	The risk of hyperkalemia may be increased when aliskiren is coadministered with potassium-sparing diuretics. Decreased aldosterone activity by aliskiren may function synergistically with potassium conservation by potassium-sparing diuretics leading to the development of hyperkalemia.
Amiloride	2	Macrolide immunosuppressants	Macrolide immunosuppressives and potassium-sparing diuretics may exert additive effects on potassium leading to hyperkalemia.
Hydrochlorothiazide	2	Diazoxide	Hyperglycemia may occur with symptoms similar to diabetes. The mechanism is unknown.
Hydrochlorothiazide	2	Digitalis glycosides	Diuretic-induced electrolyte disturbances may predispose the patient to digitalis-induced cardiac arrhythmias.
Triamterene	2	Indomethacin and derivatives	The combination of indomethacin and derivatives and triamterene may cause a sudden onset of nephrotoxicity.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the potassium-sparing diuretics are listed in Table 6. The boxed warning for amiloride is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Potassium-Sparing Diuretics[1-6]

Adverse Events	Amiloride	Amiloride/ Hydrochlorothiazide	Triamterene/ Hydrochlorothiazide
Cardiovascular			
Arrhythmia	≤1	≤1	✔
Bradycardia	-	-	1-10
Chest pain	≤1	≤1	-
Congestive heart failure	-	-	1-10
Edema	-	-	1-10
Hypotension	-	1-10	1-10

Adverse Events	Amiloride	Amiloride/ Hydrochlorothiazide	Triamterene/ Hydrochlorothiazide
Orthostatic hypotension	≤1	1-10	1-10
Palpitations	≤1	≤1	-
Central Nervous System			
Dizziness	1-10	1-10	1-10
Fatigue	1-10	1-10	1-10
Headache	1-10	1-10	1-10
Dermatological			
Alopecia	≤1	≤1	≤1
Erythema multiforme	-	≤1	≤1
Exfoliative dermatitis	-	≤1	≤1
Photosensitivity	-	1-10	1-10
Rash	-	-	1-10
Stevens-Johnson syndrome	-	<1	<1
Toxic epidermal necrolysis	-	<1	<1
Endocrine and Metabolic			
Dehydration	1-10	1-10	<1
Gynecomastia	1-10	1-10	<1
Metabolic acidosis	1-10	1-10	<1
Postmenopausal bleeding	-	-	<1
Gastrointestinal			
Abdominal pain	1-10	1-10	✔
Anorexia	-	1-10	1-10
Appetite changes	1-10	1-10	-
Constipation	1-10	1-10	1-10
Diarrhea	1-10	1-10	✔
Epigastric distress	-	1-10	1-10
Flatulence	≤1	≤1	-
Gastrointestinal bleeding	≤1	≤1	-
Nausea	1-10	1-10	1-10
Pancreatitis	-	<1	<1
Vomiting	1-10	1-10	✔
Genitourinary			
Bladder spasms	≤1	≤1	-
Dysuria	≤1	≤1	-
Impotence	1-10	1-10	<1
Polyuria	≤1	≤1	-
Renal dysfunction	-	≤1	≤1
Hematological			
Agranulocytosis	-	≤1	≤1
Aplastic anemia	-	≤1	≤1
Hemolytic anemia	-	<1	<1
Leukopenia	-	≤1	≤1
Thrombocytopenia	-	≤1	≤1
Laboratory Test Abnormalities			
Hypercalcemia	-	<1	<1
Hyperkalemia	<10	-	-
Hypokalemia	-	1-10	1-10
Hyponatremia	1-10	1-10	1-10
Musculoskeletal			
Muscle cramps	1-10	1-10	✔
Weakness	1-10	1-10	✔
Renal			
Interstitial nephritis	-	<1	<1

Adverse Events	Amiloride	Amiloride/ Hydrochlorothiazide	Triamterene/ Hydrochlorothiazide
Renal failure	-	<1	<1
Respiratory			
Cough	1-10	1-10	-
Dyspnea	1-10	1-10	1-10
Eosinophilic pneumonitis	-	<1	<1
Respiratory distress	-	<1	<1
Other			
Allergic myocarditis	-	<1	<1
Allergic reactions	-	<1	<1
Hepatic function impairment	-	<1	<1
Increased intraocular pressure	≤1	≤1	-
Jaundice	≤1	≤1	-
Tinnitus	≤1	≤1	-
Visual disturbance	-	≤1	≤1

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Amiloride[1]

WARNING
Hyperkalemia: Like other potassium-conserving agents, amiloride may cause hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly (about 10%) when amiloride is used without a kaliuretic diuretic. This incidence is greater in patients with renal impairment, diabetes mellitus (with or without recognized renal insufficiency), and in the elderly. When amiloride is used concomitantly with a thiazide diuretic in patients without these complications, the risk of hyperkalemia is reduced to about 1% to 2%. It is thus essential to monitor serum potassium levels carefully in any patient receiving amiloride, particularly when it is first introduced, at the time of diuretic dosage adjustments, and during any illness that could affect renal function.

VII. Dosing and Administration

The usual dosing regimens for the potassium-sparing diuretics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Potassium-Sparing Diuretics[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amiloride	Edema/Hypertension: Initial: 5 mg daily; may increase to 10 mg daily if needed; maximum, 20 mg	Safety and efficacy in children have not been established.	Tablet: 5 mg
Amiloride and hydrochlorothiazide	Edema/Hypertension: Initial: 5 mg-50 mg once daily; maintenance, 5 mg-50 mg to 10 mg-100 mg once daily or in divided doses	Safety and efficacy in children have not been established.	Tablet: 5 mg-50 mg
Triamterene and hydrochlorothiazide	Edema/Hypertension: Initial: 37.5 mg-25 mg once daily; maintenance: 37.5 mg-25 mg to 75 mg-50 mg once daily	Safety and efficacy in children have not been established.	Capsule: 37.5 mg-25 mg 50 mg-25 mg Tablet: 37.5 mg-25 mg 75 mg-50 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the potassium-sparing diuretics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Potassium-Sparing Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Edema/Heart Failure				
Bayliss et al.[23] (1987) Amiloride 5 mg QD and furosemide 40 mg	OS Patients with heart failure, 22 to 75 years of age, referred with breathlessness on moderate exertion (NYHA class II-III) who were not previously treated	N=12 1 month	Primary: Average weight, heart rate at rest and maximal exercise, maximal treadmill exercise time, plasma renin, plasma aldosterone, noradrenaline at rest and maximal exercise	Primary: Average weight was significantly reduced during treatment from 72.4 to 68.5 kg (P=0.0003). Resting heart rate decreased from 89 to 75 bpm (P=0.03). There was no significant change during exercise. Maximal treadmill exercise time significantly increased from 9.1 to 17.6 minutes (P=0.007). Plasma concentrations of renin increased from 1.1 to 4.2 ng/mL/hr at rest and from 2.5 to 11.3 ng/mL/hr upon exercise (P<0.007). Plasma concentrations of aldosterone increased from 169 to 488 pmol/L at rest and from 223 to 737 pmol/L upon exercise (P<0.007). Plasma concentrations of noradrenaline were significantly reduced (decreased to within normal ranges) at rest following treatment (P=0.005) but remained abnormally high at maximal exercise following treatment.
Rengo et al.[24] (1979) Amiloride 15 mg QD vs amiloride 15 mg QD and HCTZ 150 mg QD (combination	RCT Patients 35 to 60 years of age with liver cirrhosis and ascites or congestive heart failure	N=30 15 days	Primary: Body weight, 24 hour diuresis, serum sodium, serum potassium, sodium and potassium urinary loss	Primary: All groups had a statistically significant reduction in body weight from baseline (P<0.001, all groups). Combination amiloride-HCTZ showed a significantly greater reduction compared to amiloride alone (P<0.001). All groups significantly differed from baseline in 24 hour diuresis (P<0.01). Amiloride-HCTZ and HCTZ resulted in more diuresis than amiloride (P<0.001, for both). Serum sodium was reduced from baseline in all groups. HCTZ alone had a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
entity) vs HCTZ 150 mg QD				significantly greater reduction than amiloride (P<0.01), and amiloride-HCTZ (P<0.001). Sodium urinary loss was seen in all treatments at day 2, amiloride-HCTZ had maintained this loss at day 5 (P<0.001, for both). Serum potassium decreased in the HCTZ group but increased in the amiloride and amiloride-HCTZ groups. HCTZ alone resulted in a marked increase in potassium urinary loss (P<0.001).
Cheitlin et al.[25] (1991) Amiloride 5 or 10 mg QD for 7 days, placebo QD for the next 14 days, along with HCTZ 50 or 100 mg QD (separate entities) vs placebo QD for 14 days, amiloride 5 or 10 mg QD for the next 7 days, along with HCTZ 50 or 100 mg QD (separate entities)	DB, PC, RCT, XO Patients with an average age of 63 and a history of congestive heart failure and ≥1 episode of pulmonary edema (NYHA class II-III) who were not previously treated	N=11 21 days	Primary: Hemodynamic changes at rest and exercise	Primary: At rest, there were no significant differences between patients treated with placebo or amiloride in right atrial pressure, pulmonary atrial pressure, heart rate, pulmonary artery wedge pressure, systemic arterial pressure, right ventricular stroke work index, left ventricular stroke work index, systemic vascular resistance, cardiac index, or stroke volume index. During exercise, there were significant differences between patients treated with placebo or amiloride at the 50-watt stage in right atrial pressure (15.0 vs 10.5 mm Hg), pulmonary artery wedge pressure (28.6 vs 22.1 mm Hg), pulmonary artery diastolic pressure (32.2 vs 21.6 mm Hg), mean pulmonary artery pressure (44.4 vs 38.9 mm Hg), left ventricular stroke work index (69.5 vs 77.9 g-m/m^2), and stroke volume index (44.9 vs 46.2 cc/beat/m^2), respectively. There were no significant differences between placebo and amiloride during exercise in right ventricular stroke work index, heart rate, aortic pressure, cardiac index, and total systemic vascular resistance.
Ghosh et al.[29] (1987) Amiloride 2.5 mg QD and HCTZ 25 mg QD (combination entity) vs	PG, RCT, SB Elderly patients (mean age 80) with stable, mild to moderate congestive heart failure	N=60 8 weeks	Primary: Body weight, clinical score, biochemistry	Primary: Body weight was reduced in both treatment groups. Both treatments resulted in improvements in clinical scores; 95% of the amiloride-HCTZ group and 88% of the triamterene-HCTZ group showed an improvement in heart failure signs with no patient's symptoms becoming worse. 85% of the amiloride-HCTZ group and 84% of the triamterene-HCTZ group showed an improvement in heart failure symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
triamterene 50 mg QD and HCTZ 25 mg QD (combination entity)				There were no significant between group differences in serum sodium, potassium, or urea.
Faris et al.[22] (2006) Potassium-sparing diuretics (amiloride, triamterene), loop diuretics (furosemide, bumetanide), or thiazide diuretics (chlorothiazide) vs placebo or active control (ACE inhibitors, digoxin)	MA Adult patients with chronic heart failure	N=525 (14 trials) 2 to 52 weeks	Primary: Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Primary: Mortality was reported in 3 of the 7 placebo-controlled trials, and this analysis showed that mortality was lower for patients treated with diuretics than with placebo (3/111[2.7%] vs 12/110 [10.9%], respectively; OR 0.24; 95% CI, 0.07 to 0.83; P=0.02). These results showed that patients treated with diuretics had an absolute risk reduction of 8% when compared to placebo and a number needed to treat of 12.5. Secondary: An analysis of pooled data from 2 trials showed lower admission rates for worsening heart failure in patients taking diuretics than in patients taking placebo (OR 0.07; 95% CI, 0.01 to 0.52; P=0.01). Diuretics were found to improve exercise capacity, with a difference in means of 0.74 (95% CI, 0.37 to 1.11; P<0.0001) and of 0.67 (95% CI, 0.02 to 1.31; P=0.04.), respectively. The combined results of these 4 trials indicated that diuretics improved exercise capacity in participants with chronic heart failure with a difference in means of 0.72 (95% CI, 0.40 to 14; P<0.0001).
Hypertension				
Multicenter Diuretic Cooperative Study Group[27] (1981) Amiloride 5 mg QD	DB, MC, RCT Patients 21 to 69 years of age with mild to moderate essential hypertension (supine DBP 95 to 115 mm Hg)	N=179 12 weeks	Primary: Change from baseline in average supine SBP and DBP Secondary: Heart rate, body weight, serum	Primary: Baseline vs 12-week average supine blood pressure was 153/101 vs 139/93 mm Hg for amiloride, 160/100 vs 137/90 mm Hg for amiloride-HCTZ, and 154/101 vs 134/89 mm Hg for HCTZ. Reductions in supine blood pressure was significant in all treatment groups (P<0.01). The SBP reduction was greater with amiloride-HCTZ than with amiloride at all weeks and HCTZ at 4 and 8 weeks (P<0.05, both). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amiloride 5 mg and HCTZ 50 mg QD (combination entity) vs HCTZ 50 mg QD			potassium	No significant changes from baseline in heart rate were observed with amiloride or HCTZ. An increase in heart rate was observed with amiloride-HCTZ of 3.3 bpm (P<0.05). Changes in body weight from baseline were –1.17 kg for amiloride-HCTZ, –0.72 kg for HCTZ, and 0.045 kg for amiloride (P<0.05, for amiloride-HCTZ only). Changes in serum potassium from baseline were 0.23 mEq/L for amiloride (P<0.01), –0.38 mEq/L for amiloride-HCTZ (P<0.01), and –0.59 mEq/L for HCTZ (P<0.01). The HCTZ change was statistically greater than the amiloride-HCTZ change (P<0.05). Nearly 23% of HCTZ, 2% of amiloride-HCTZ, and 0% of amiloride patients experienced hypokalemia.
Salmela et al.[26] (1986) Amiloride 2.5 mg and HCTZ 25 mg daily vs HCTZ 25 mg daily	DB, MC, PG, RCT Men and women with mild to moderate hypertension, mean 66.7 years of age	N=40 12 weeks	Primary: Changes in blood pressure	Primary: At the end of the first treatment period, mean supine SBP and DBP was 161 and 91 mm Hg for subjects receiving combination treatment; from baseline week 4; P<0.01 and P<0.001, respectively. At the end of the first treatment period, mean supine SBP and DBP was 165 and 96 mm Hg for subjects receiving HCTZ monotherapy; P<0.01, from baseline week 4 to the end of the first treatment period. At the end of the second treatment period, mean supine SBP and DBP was 154 and 86 mm Hg for subjects receiving combination treatment; from baseline week 4 to the end of the second treatment period; P<0.01 and P<0.001. At the end of the second treatment period, mean supine SBP and DBP was 155 and 90 mm Hg for subjects receiving HCTZ monotherapy; for both; P<0.001 from baseline week 4 to the end of the second treatment period. There were no statistically significant differences in blood pressure reduction between the 2 groups.
Kohvakka et al.[28] (1979) Amiloride 5 mg	PC, RCT, XO Patients 41 to 70 years of age with	N=31 3 months	Primary: Changes in blood pressure, serum potassium, sodium,	Primary: No significant changes in blood pressure were observed with any of the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD and HCTZ 50 mg QD (combination entity) vs triamterene 75 mg QD and HCTZ 50 mg QD (combination entity) vs potassium chloride 1,500 mg QD and HCTZ 50 mg QD (separate entities) vs spironolactone 50 mg QD and HCTZ 50 mg QD (separate entities) vs placebo	uncomplicated hypertension, previously treated with antihypertensive agents for 1 to 6 years		creatinine, urate, total body potassium	Mean serum potassium was reduced in all active treatment groups except with the spironolactone group. KCl supplementation was least effective in elevating serum potassium. Total body potassium remained constant throughout treatment. Serum sodium remained within normal limits in all treatment groups. There were no significant changes in mean serum creatinine in any of the treatment groups. Serum urate concentration increased significantly in all treatment groups including HCTZ alone.
Larochelle et al.[30] (1985) Amiloride 5 mg and HCTZ 50 mg vs	DB, RCT Ambulant patients, 18 to 70 years of age with essential hypertension who after not being	N=266 8 weeks	Primary: Blood pressure and serum potassium concentration	Primary: At 8 weeks, there were no statistically significant differences between groups in the mean blood pressure reductions. During the 8 weeks of treatment, the group receiving combination therapy experienced a decrease in the mean supine blood pressure and mean serum potassium level. Respectively these reductions were from 156/99 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 50 mg	treated for at least 2 weeks prior to the study had a supine DBP of 95 to 109 mm Hg and a serum potassium level of >3.5 mmol/L			138/88 mm Hg and from 4.23 to 3.91 mmol/L. During the 8 weeks of treatment, the monotherapy group experienced a reduction in the mean supine blood pressure and mean serum potassium level; respectively from 157/99 to 138/87 mm Hg and from 4.16 to 3.69 mmol/L. Hypokalemia occurred less frequently in the combination group than in the monotherapy group (14% and 29%; P=0.0026). However, the proportions of patients with a potassium level exceeding 4.5 mmol/L were similar 4.5% and 3.9%, respectively.
Dean et al.[31] (1984) Amiloride 5 mg QD and HCTZ 50 mg QD (combination entity) vs triamterene 50 mg QD and HCTZ 25 mg QD (combination entity)	RCT, SB, XO Patients with mild to moderate hypertension (DBP 95 to 110 mm Hg)	N=20 8 weeks	Primary: Blood pressure, hypokalemia, hyperkalemia, renal function tests	Primary: The treatments produced a comparable effect on blood pressure. The baseline standing and lying blood pressure was 168/105 and 168/104 mm Hg, respectively. At week 8 of amiloride-HCTZ treatment, the standing and lying blood pressure was 145/92 and 145/90 mm Hg, respectively. At week 8 of triamterene-HCTZ treatment, the standing and lying blood pressure was 142/93 and 143/91 mm Hg, respectively. There were no cases of hypokalemia or hyperkalemia and no renal function changes in either group.
Maxwell et al.[32] (1985) Amiloride and HCTZ 1 tablet daily vs triamterene and	OL, PRO, randomized Subjects with mild to moderate hypertension, mean supine DBP <90 mm Hg or >114 mm Hg at the end of the 3-week placebo	N=84 9 weeks	Primary: Mean blood pressure changes	Primary: Of all subjects participating, 73% (30 subjects) of the triamterene-HCTZ group and 81% (35 subjects) of the amiloride-HCTZ group were maintained on one capsule or tablet daily throughout the study; no significant differences between treatment groups. At week 9, mean SBP and DBP was 136.2 and 87.4 mm Hg with triamterene-HCTZ. At week 9, mean SBP and DBP was 132.6 and 85.7 mm Hg with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
HCTZ 1 capsule daily	phase			amiloride-HCTZ. At week 9, mean serum potassium levels were 4.13 mEq/L with triamterene-HCTZ and 3.98 mEq/l with amiloride-HCTZ (P value <0.05 for the difference between the regimens).
Williams et al.[33] (1984) Phase 1 Triamterene 37.5 mg-HCTZ 25 mg (Dyazide®), 2 capsules/day vs triamterene 37.5 mg-HCTZ 25 mg (Dyazide®), 4 capsules/day vs no antihypertensive medications Phase 2 Triamterene 75 mg-HCTZ 50 mg (Maxzide®) 1 tablet daily Phase 3 Triamterene 75 mg-HCTZ 50 mg (Maxzide®) 1	OL Patients 21 to 70 years of age, with essential hypertension	N=156 6 to 32 weeks	Primary: Blood pressure and weight comparisons between phase 1 and phase 2 Secondary: Serum potassium concentrations	Primary: During phase 1, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 2 Dyazide® capsules daily as prior therapy (Group 1) were: 91 mm Hg, 138 mm Hg, and 82 kg. During phase 2, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 2 Dyazide® capsules daily as prior therapy (Group 1) were: 88 mm Hg, 135 mm Hg, and 82 kg. During phase 1, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 4 Dyazide® capsules daily as prior therapy (Group 2) were: 93 mm Hg, 139 mm Hg, and 87 kg. During phase 2, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking 4 Dyazide® capsules daily as prior therapy (Group 2) were: 98 mm Hg, 149 mm Hg, and 79 kg. During phase 1, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking no prior therapy (Group 3) were: 98 mm Hg, 149 mm Hg, and 80 kg. During phase 2, comparisons of mean standing DBP, mean standing SBP, and weight comparisons for subjects taking no prior therapy (Group 3) were: 94 mm Hg, 136 mm Hg, and 78 kg. Of these phase 1 and phase 2 comparisons, mean standing DBP and SBP differences were reported to be statistically significant during phase 2 for those subjects taking 2 Dyazide® capsules daily as prior therapy (Group 1) and for those subjects taking no prior therapy (Group 3). Additionally, the investigators concluded that patients with mild to moderate hypertensive who were taking 2 or 4 capsules of Dyazide® daily

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tablet daily				or no antihypertensive medications could be transferred safely to the combination of triamterene and HCTZ (Maxzide® 75/50 mg). Secondary: When patient taking Dyazide® 4 capsules/day were switched to Maxzide® 1 tablet daily, no patient became hypokalemic (serum potassium concentration <3.5 mEq/L) while taking the thiazide.

Drug regimen abbreviations: HCTZ=hydrochlorothiazide, KCl=potassium chloride, QD=once daily
Study abbreviations: DB=double-blind, MA=metaanalysis, MC=multicenter, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Miscellaneous abbreviations: bpm=beats per minute, DBP=diastolic blood pressure, NYHA=New York Heart Association, SBP=systolic blood pressure

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 10. Relative Cost of the Potassium-Sparing Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amiloride	tablet	Midamor®*	$$$	$$$
Amiloride and hydrochlorothiazide	tablet	N/A	N/A	$
Triamterene and hydrochlorothiazide	capsule, tablet	Dyazide®*, Maxzide®*	$$	$-$$

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

X. Conclusions

The potassium-sparing diuretics are approved for the treatment of congestive heart failure, edema and hypertension.[1-6] When used alone, amiloride has a weak diuretic and antihypertensive effect and increases the risk of hyperkalemia.[4] It should be used alone only when persistent hypokalemia has been documented. The potassium-sparing diuretics are generally used in combination with other diuretics to help restore normal serum potassium levels or to prevent the development of hypokalemia. Amiloride and triamterene are available as a fixed-dose combination with hydrochlorothiazide. All of the products are available in a generic formulation.

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload.[11-13] The loop diuretics are generally recommended as initial therapy in patients with left ventricular dysfunction.[12-13] For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[11-12] Aldosterone antagonists should always be preferred over the use of other potassium-sparing diuretics.[13]

There are several national and international organizations that have published guidelines on the treatment of hypertension.[14-21] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension.[14-15,17,21] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[16,18] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[16,18] Guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[14-21] Most patients will need more than one antihypertensive medication to achieve blood pressure goals. The use of a fixed-dose combination product may simplify the treatment regimen and improve adherence.[16,18] However, there are no prospective, randomized trials that have demonstrated better clinical outcomes with a fixed-dose combination product compared to the coadministration of the individual components as separate formulations.

Amiloride has been shown to be effective for the treatment of edema, hypertension, as well as for the prevention of serum potassium loss in patients taking a thiazide or loop diuretic.[23-27,30] Clinical studies have also demonstrated comparable efficacy with the fixed-dose combination of amiloride/hydrochlorothiazide and triamterene/hydrochlorothiazide in patients with hypertension and heart failure.[28-29,31-32]

There is insufficient evidence to support that one brand potassium-sparing diuretic 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 potassium-sparing diuretics 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 potassium-sparing diuretic 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 Thiazide Diuretics
AHFS Class 402820
November 10, 2010

I. Overview

The thiazide diuretics are approved for the treatment hypertension and edema due to renal dysfunction.[1-9] They are also approved as adjunctive therapy for the management of edema associated with congestive heart failure, hepatic cirrhosis, as well as corticosteroid and estrogen therapy. The thiazide diuretics inhibit the reabsorption of sodium and chloride in the cortical thick ascending limb of the loop of Henle and the early distal tubules. This action leads to an increase in the urinary excretion of sodium and chloride in approximately equivalent amounts. Additionally, increased potassium and bicarbonate excretion, decreased calcium excretion, and uric acid retention may be observed. During initial thiazide therapy, a reduction in cardiac output and extracellular volume occurs. However, with chronic therapy, cardiac output normalizes and both peripheral vascular resistance and extracellular volume are reduced.[1] In general, similar therapeutic and adverse effects are seen when equipotent doses are used.[3] Thiazide diuretics are generally recommended when the glomerular filtration rate is above 30 mL/min.[22,24]

The thiazide diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the agents are available in a generic formulation. This class was last reviewed in September 2008.

Table 1. Thiazide Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chlorothiazide	injection, suspension, tablet	Diuril®, Diuril Sodium®*	chlorothiazide
Hydrochlorothiazide	capsule, tablet	Microzide®*	hydrochlorothiazide
Methyclothiazide	tablet	N/A	methyclothiazide

*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 thiazide diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of heart failure and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Thiazide Diuretics

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases (AASLD): **Management of Adult Patients with Ascites Due to Cirrhosis: An Update[41] (2009)**	• First-line treatment of patients with cirrhosis and ascites consists of sodium restriction and diuretics (oral spironolactone with or without oral furosemide). • The typical diuretic regimen consists of single morning doses of spironolactone, beginning with 100 mg, in addition to furosemide 40 mg. Single morning dosing improves adherence. • Spironolactone monotherapy may be used only in patients who have minimal fluid overload. • In patients experiencing painful gynecomastia with spironolactone, amiloride may be an appropriate substitute. However, amiloride has been shown to be less effective than an active metabolite of spironolactone. • Triamterene, metolazone, and hydrochlorothiazide have also been used

Clinical Guideline	Recommendation(s)
	to treat ascites. Hydrochlorothiazide can also cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses.
World Gastroenterology Organization (WGO) Practice Guideline: **Management of Ascites Complicating Cirrhosis in Adults**[42]	• Initial oral diuretic therapy consists of single daily doses of spironolactone or spironolactone in addition to furosemide. • Spironolactone monotherapy is more effective compared to furosemide monotherapy. However its use should be restricted to patients exhibiting minimal fluid overload. • Spironolactone monotherapy may be complicated by hyperkalemia and gynecomastia. Amiloride and triamterene are substitutes for spironolactone. • Indications of diuretic resistance include minimal to no weight loss and urinary sodium excretion of <78 mmol/day. Diuretic therapy should be discontinued in patients who develop encephalopathy, clinically significant complications of diuretics, hyperkalemia, metabolic acidosis with spironolactone, and whose serum sodium is <120 mmol/L or serum creatinine >2 mg/dL.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline**[15] **(2010)**	<u>Patients With Left Ventricular Systolic Dysfunction</u> • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • Torsemide may be considered in patients in whom erratic diuretic effect or absorption is present, particularly those with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • The addition of metolazone or chlorothiazide to loop diuretics should be considered in patients with persistent fluid retention despite high-dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion. • Patients requiring diuretic therapy to treat fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • Diuretic treatment is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. <u>Patients With Acute Decompensated Heart Failure (ADHF)</u> • It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally. • Intravenous vasodilators and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe

Clinical Guideline	Recommendation(s)
	hypertension. Patients With Heart Failure and Hypertension • The use of an ACE inhibitor is recommended. • The addition of a β-blocker is recommended even if blood pressure is controlled. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine CCB (e.g., amlodipine or felodipine) or other antihypertensive drugs.
American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults**[13] **(2009)**	Patients at Risk for Developing Heart Failure (Stage A) • Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. Patients With Refractory End-Stage Heart Failure (Stage D) • Treatment of fluid retention is important. Hospitalized Patients • For patients admitted with heart failure who have evidence of significant fluid overload, intravenous loop diuretics should be started as soon as possible in the emergency department. If patients are already receiving loop diuretics, the initial intravenous dose should equal or exceed their chronic daily oral dose. • When diuresis is inadequate to relieve congestion, the diuretic regimen should be intensified using either a higher dose of loop diuretic, addition of a second diuretic, or continuous infusion of a loop diuretic.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure**[16] **(2008)**	Pharmacologic Therapy of Chronic Heart Failure • Diuretics are recommended in patients with heart failure and clinical signs or symptoms of congestion. • Diuretics cause activation of the renin–angiotensin–aldosterone system in patients with mild symptoms of heart failure and should usually be used in combination with an ACE inhibitor or ARB. • In general, a loop diuretic will be required in moderate or severe heart failure. A thiazide may be used in combination with loop diuretics for resistant edema, but with caution to avoid dehydration, hypovolemia, hyponatremia, or hypokalemia. Management of Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (HFPEF) • Diuretics are used to control sodium and water retention and relieve shortness of breath and edema.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management**[19] **(2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific

Clinical Guideline	Recommendation(s)
	cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[18] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[20] (2006)**	• Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.

Clinical Guideline	Recommendation(s)
	• If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7)[14] (2004)**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2-4 times higher in African American patients. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[24] (2004)**	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be

Clinical Guideline	Recommendation(s)
	considered to increase patient adherence.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension[17] (2003)**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans[23] (2003)**	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[22] (2010)**	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed, a thiazide diuretic may be added if estimated glomerular filtration rate (GFR) is ≥30 ml/min/1.73 m^2 or a loop diuretic for patients whose estimated GFR is <30 ml/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the thiazide diuretics 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 Thiazide Diuretics[1-9]

Indication	Chlorothiazide	Hydrochlorothiazide	Methyclothiazide
Edema			
Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy	✔	✔ †	✔
Treatment of edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure	✔	✔ †	✔
Hypertension			
Treatment of hypertension	✔ *	✔ *	✔ *

*Alone or in combination with other antihypertensive agents.
†Tablet formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the thiazide diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Thiazide Diuretics[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Chlorothiazide	Poor	Not reported	Not metabolized	Renal (96)	45-120 min
Hydrochlorothiazide	50-75	40-68	Not metabolized	Renal (>95)	6-15
Methyclothiazide	Not reported	Not reported	Not reported	Renal	Not reported

V. Drug Interactions

Significant drug interactions with the thiazide diuretics are listed in Table 5.

Table 5. Significant Drug Interactions with the Thiazide Diuretics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Chlorothiazide	1	Disulfiram	Co-administration of chlorothiazide and disulfiram may produce acute and severe alcohol intolerance. Inhibition of aldehyde dehydrogenase by disulfiram leads to the development of toxic intermediate metabolites.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	1	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide	1	Lithium	Thiazide diuretics may promote enhanced proximal tubular reabsorption of lithium leading to elevated serum concentrations. Thiazide diuretics may increase the therapeutic and toxic effects of lithium.
Chlorothiazide	2	Metronidazole	The combination of metronidazole and chlorothiazide may produce alcohol intolerance reactions. Metronidazole may inhibit aldehyde dehydrogenase-medicated metabolism of ethanol and cause a toxic accumulation of acetaldehyde.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	2	Diazoxide	The combination of diazoxide with a thiazide diuretic may lead to hyperglycemia though an unknown mechanism; therefore the combination should be avoided.
Thiazides (chlorothiazide, hydrochlorothiazide, methyclothiazide)	2	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the thiazide diuretics are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Thiazide Diuretics[1-9]

Adverse Events	Chlorothiazide	Hydrochlorothiazide	Methyclothiazide
Cardiovascular			
Hypotension	✔	1-10	1-10
Necrotizing angiitis	✔	-	<1
Orthostatic hypotension	✔	1-10	1-10
Central Nervous System			
Dizziness	✔	-	-
Fever	✔	-	-
Headache	✔	-	-
Restlessness	✔	-	-
Vertigo	✔	-	-
Dermatological			
Alopecia	✔	<1	-
Cutaneous vasculitis	-	-	<1
Erythema multiforme	✔	<1	<1
Exfoliative dermatitis	✔	<1	-
Photosensitivity	✔	1-10	1-10
Purpura	✔	-	-
Rash	✔	-	-
Stevens-Johnson syndrome	✔	<1	<1
Toxic epidermal necrolysis	✔	<1	-
Urticaria	✔	-	-
Vasculitis	-	-	<1
Gastrointestinal			
Abdominal cramping	✔	-	-
Anorexia	✔	1-10	1-10
Constipation	✔	-	-
Diarrhea	✔	-	-
Epigastric distress	-	1-10	1-10
Gastric irritation	✔	-	-
Nausea	✔	-	-
Pancreatitis	✔	<1	<1
Sialadenitis	✔	-	-
Vomiting	✔	-	-
Genitourinary			
Impotence	✔	-	-
Hematologic			
Agranulocytosis	✔	<1	<1
Aplastic anemia	✔	<1	<1
Hemolytic anemia	✔	-	<1
Leukopenia	✔	<1	<1
Thrombocytopenia	✔	<1	<1
Hepatic			
Hepatic function impairment	-	<1	<1
Jaundice	✔	-	-
Laboratory Test Abnormalities			
Cholesterol increased	✔	-	-
Hypercalcemia	-	<1	<1
Hyperglycemia	✔	-	-
Hyperuricemia	✔	-	-

Adverse Events	Chlorothiazide	Hydrochlorothiazide	Methyclothiazide
Hypochloremic alkalosis	✔	-	-
Hypokalemia	✔	1-10	1-10
Hypomagnesemia	✔	-	-
Hyponatremia	✔	-	-
Triglycerides increased	✔	-	-
Musculoskeletal			
Muscle spasm	✔	-	-
Paresthesia	✔	-	-
Weakness	✔	-	-
Ocular			
Blurred vision	✔	-	-
Xanthopsia	✔	-	-
Renal			
Glycosuria	✔	-	-
Interstitial nephritis	✔	<1	-
Renal dysfunction	✔	-	-
Renal failure	✔	<1	-
Respiratory			
Pneumonitis	✔	-	-
Pulmonary edema	✔	-	-
Respiratory distress	✔	<1	<1
Other			
Allergic myocarditis	-	<1	-
Allergic reactions	-	<1	-
Anaphylactic reactions	✔	<1	-
Eosinophilic pneumonitis	-	<1	-
Systemic lupus erythematosus	✔	-	-

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

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

Table 7. Usual Dosing Regimens for the Thiazide Diuretics[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chlorothiazide	Edema: 0.5 to 1 g once or twice daily, often administered on alternate days or on three to five days each week Hypertension: Initial: 0.5 or 1 g daily as a single dose or in divided doses; adjust according to blood pressure response; some patients may require up to 2 g a day in divided doses	Diuresis and Control of Hypertension: 10 to 20 mg/kg daily in a single or two divided doses; maximum 375 mg daily (infants up to 2 years old)or 1 g daily (children 2 to 12 years old)	Injection: 500 mg Suspension, oral: 250 mg/5 ml Tablet: 250 mg 500 mg
Hydrochlorothiazide	Edema: 25 to 100 mg daily in single or divided doses Hypertension:	Diuresis and Control of Hypertension: 1 to 2 mg/kg daily in a single or two divided doses; maximum, 37.5 mg daily	Capsule: 12.5 mg Tablet: 12.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Initial: 12.5 to 25 mg once daily; maintenance, 50 to 100 mg daily in single or divided doses	(infants up to 2 years old) or 100 mg daily (children 2 to 12 years old)	25 mg 50 mg
Methyclothiazide	Edema: 2.5 to 10 mg once daily; maximum, 10 mg daily Hypertension: 2.5 to 5 mg once daily	Safety and efficacy in children have not been established.	Tablet: 5 mg

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with the Thiazide Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Edema				
Cheitlin et al.[29] (1991) Amiloride 5 or 10 mg QD for 7 days, placebo QD for the next 14 days, along with HCTZ 50 or 100 mg QD (separate entities) vs placebo QD for 14 days, amiloride 5 or 10 mg QD for the next 7 days, along with HCTZ 50 or 100 mg QD (separate entities)	DB, PC, RCT, XO Patients with an average age of 63 and a history of congestive heart failure and ≥1 episode of pulmonary edema (NYHA class II-III) who were not previously treated	N=11 21 days	Primary: Hemodynamic changes at rest and exercise	Primary: At rest, there were no significant differences between patients treated with placebo or amiloride in right atrial pressure, pulmonary atrial pressure, heart rate, pulmonary artery wedge pressure, systemic arterial pressure, right ventricular stroke work index, left ventricular stroke work index, systemic vascular resistance, cardiac index, or stroke volume index. During exercise, there were significant differences between patients treated with placebo or amiloride at the 50-watt stage in right atrial pressure (15.0 vs 10.5 mm Hg), pulmonary artery wedge pressure (28.6 vs 22.1 mm Hg), pulmonary artery diastolic pressure (32.2 vs 21.6 mm Hg), mean pulmonary artery pressure (44.4 vs 38.9 mm Hg), left ventricular stroke work index (69.5 vs 77.9 g-m/m^2), and stroke volume index (44.9 vs 46.2 cc/beat/m^2), respectively. There were no significant differences between placebo and amiloride during exercise in right ventricular stroke work index, heart rate, aortic pressure, cardiac index, and total systemic vascular resistance.
Rengo et al.[27] (1979) HCTZ 150 mg QD vs amiloride 15 mg QD vs	RCT Patients 35 to 60 years of age with liver cirrhosis and ascites or congestive heart failure	N=30 15 days	Primary: Body weight, 24 hour diuresis, serum sodium, serum potassium, sodium and potassium urinary loss	Primary: All groups had a statistically significant reduction in body weight from baseline (P<0.001, all groups). Combination amiloride-HCTZ showed a significantly greater reduction compared to amiloride alone (P<0.001). All groups significantly differed from baseline in 24 hour diuresis (P<0.01). Amiloride-HCTZ and HCTZ resulted in more diuresis than amiloride (P<0.001, for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amiloride 15 mg QD and HCTZ 150 mg QD (combination entity)				Serum sodium was reduced from baseline in all groups. HCTZ alone had a significantly greater reduction than amiloride (P<0.01), and amiloride-HCTZ (P<0.001). Sodium urinary loss was seen in all treatments at day 2, amiloride-HCTZ had maintained this loss at day 5 (P<0.001, for both). Serum potassium decreased in the HCTZ group but increased in the amiloride and amiloride-HCTZ groups. HCTZ alone resulted in a marked increase in potassium urinary loss (P<0.001).
Kohvakka[28] (1988) HCTZ 50 mg BID vs amiloride 5 mg BID and HCTZ 50 mg BID (combination entity) vs triamterene 75 mg BID and HCTZ 50 mg BID (combination entity) vs potassium chloride 1 g BID and HCTZ 50 mg BID (separate entities)	RCT, XO Patients 41 to 69 years of age with congestive heart failure (NYHA class II-III), average cardiac failure duration of 9.3 years, average previous diuretic treatment duration of 6.8 years, developed persistent hypokalemia on HCTZ alone	N=25 5 months	Primary: Changes in weight, blood pressure, serum sodium, serum potassium, total body potassium Secondary: Percentage with hypokalemia, median days until hypokalemia detection, serum magnesium	Primary: Weight loss was statistically significant in the amiloride-HCTZ and triamterene-HCTZ groups (P=0.05, both groups) but not in the KCl-HCTZ group compared to HCTZ alone. No statistically significant changes in blood pressure were observed. No statistically significant differences in serum sodium were observed in the amiloride-HCTZ or triamterene-HCTZ groups. Serum sodium was slightly higher in the KCl-HCTZ group compared to HCTZ alone (P=0.01). Serum potassium was found to be significantly higher in all treatment groups compared to HCTZ alone (P=0.01, for all groups). Total body potassium was significantly higher with amiloride-HCTZ and triamterene-HCTZ (P=0.05, both groups) but not with KCl-HCTZ compared to HCTZ alone. Secondary: The percentages of patients that became hypokalemic were 39% in the amiloride-HCTZ group, 52% in the triamterene-HCTZ group, and 52% in KCl-HCTZ group. The median days until hypokalemia detection were 114 for amiloride-HCTZ, 75 for triamterene-HCTZ, and 51.5 for KCl-HCTZ. Serum magnesium was maintained at a statistically higher rate with amiloride-HCTZ and triamterene-HCTZ than with KCl-HCTZ.
Faris et al.[26]	MA	N=525	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2006) Thiazide diuretics (chlorothiazide), loop diuretics (furosemide, bumetanide), or potassium-sparing diuretics (amiloride, triamterene) vs placebo or active control (ACE inhibitors, digoxin)	Adult patients with chronic heart failure	2 to 52 weeks	Mortality Secondary: Effect of diuretic withdrawal on worsening of heart failure and exercise capacity	Mortality was reported in 3 of the 7 placebo-controlled trials, and this analysis showed that mortality was lower for patients treated with diuretics than with placebo (3/111[2.7%] vs 12/110 [10.9%], respectively; OR, 0.24; 95% CI, 0.07 to 0.83; P=0.02). These results showed that patients treated with diuretics had an absolute risk reduction of 8% when compared to placebo and a number needed to treat of 12.5. Secondary: An analysis of pooled data from 2 trials showed lower admission rates for worsening heart failure in patients taking diuretics than in patients taking placebo (OR, 0.07; 95% CI, 0.01 to 0.52; P=0.01). Diuretics were found to improve exercise capacity, with a difference in means of 0.74 (95% CI, 0.37 to 1.11; P<0.0001) and of 0.67 (95% CI, 0.02 to 1.31; P=0.04.), respectively. The combined results of these 4 trials indicated that diuretics improved exercise capacity in participants with chronic heart failure with a difference in means of 0.72 (95% CI, 0.40 to 14; P<0.0001).
Hypertension				
Hua et al.[32] (1976) Chlorothiazide up to 5 g BID vs metolazone 5 mg QD	XO Patients with hypertension	N=20 Duration not specified	Primary: Blood pressure, serum potassium	Primary: Blood pressures on metolazone tended to be lower than on chlorothiazide, but the difference was not statistically significant. Both agents significantly lowered serum potassium concentrations and total body potassium to a similar degree. However, the serum potassium did not fall below the normal range in any patient and no potassium supplements were required.
Carter et al.[33] (2004) HCTZ 12.5 to 450 mg/day	MA Included studies which evaluate the pharmacokinetic and blood pressure	N=200 Variable duration	Primary: Blood pressure Secondary: Serum potassium	Primary: In a dose equivalence study comparing HCTZ 100 mg QD to chlorthalidone 50 mg QD, blood pressure (SBP/DBP) reduced by 18/8 and 25/10 mm Hg compared to baseline, respectively. In another study comparing HCTZ 25 mg and triamterene 50 mg QD,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs chlorthalidone 12.5 to 600 mg/day	lowering effects of chlorthalidone and HCTZ			HCTZ 50 mg and triamterene 100 mg QD, and chlorthalidone 50 mg QD, the blood pressure reduction was 15/8, 18/12, and 25/16 mm Hg, respectively. One other dose equivalence study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, blood pressure reduction was 22/16 and 18/15 mm Hg, respectively. All available studies were inspected and it was concluded that HCTZ 50 mg is approximately equivalent to chlorthalidone 25 to 37 mg. Furthermore, it was suggested that chlorthalidone doses should generally be approximately 50% to 75% of the typical HCTZ dose. Secondary: In a study comparing HCTZ 100 mg QD and chlorthalidone 50 mg QD, potassium increased slightly with chlorthalidone (0.02 mEq/L) and decreased significantly with HCTZ (0.22 mEq/L; P=0.009). However, in another study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, serum potassium decreased by 0.38 mEq/L with HCTZ and by 0.03 mEq/L with chlorthalidone. The difference was not statistically significant (P<0.07).
Ernst et al.[34] (2006) HCTZ 25 mg QAM vs chlorthalidone 12.5 mg QAM At week 4, both HCTZ and chlorthalidone were titrated to 50	RCT, SB, XO Men and women aged 18 to 79 years with prehypertension or a new or established diagnosis of hypertension (stage 1 or 2), not receiving antihypertensive medications, and had an average office blood	N=30 8 weeks	Primary: Comparison of the change in 24-hour mean SBP and DBP from baseline to week 8 Secondary: Changes in mean SBP and mean DBP for office blood pressure at each visit, change in ambulatory daytime and	Primary: At week 8, there was a greater reduction in 24-hour mean SBP with chlorthalidone 25 mg/day compared to HCTZ 50 mg/day compared to baseline (−12.4±1.8 vs −7.4±1.7 mm Hg, respectively; P=0.054). Secondary: There was a trend in favor of greater reduction in SBP with chlorthalidone than with HCTZ at each office visit. However, the difference was only statistically significant at week 2 (−15.7±2.2 vs −4.5±2.1 mm Hg, respectively; P=0.001). Although mean reductions in DBP was also greater with chlorthalidone compared to HCTZ at each study visit, the differences were not statistically significant at any visit (P>0.89 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QAM and 25 mg QAM, respectively for the remainder of the study.	pressure value in the last 6 months between 140 and 179 mm Hg systolic or 90 and 109 mm Hg diastolic		nighttime mean SBP and DBP from baseline to week 8, development of hypokalemia	The reduction in SBP during nighttime hours was ─13.5±1.9 mm Hg for chlorthalidone and ─6.4±1.7 mm Hg for HCTZ (P=0.009). The reduction in daytime mean SBP between both groups was not significantly different (─11.4±2.0 vs ─8.1±1.9 mm Hg, respectively; P=0.230). Changes in serum potassium were similar between treatment groups (P=0.76). The incidence of hypokalemia was 50% in patients taking HCTZ and 46% in patients taking chlorthalidone (P=0.682).
Valmin et al.[31] (1975) HCTZ 12.5 mg BID vs furosemide 12.5, 25, or 40 mg BID vs placebo	DB, RCT, XO Men and women with essential hypertension	N=34 20 weeks	Primary: Blood pressure, urinary output, serum electrolytes, safety and tolerability	Primary: When compared to placebo, there was a significant reduction of blood pressure with HCTZ 12.5 mg twice daily and furosemide 12.5 mg twice daily (P<0.05). Paired comparison showed that HCTZ 12.5 mg twice daily and furosemide 25 and 40 mg twice daily had a similar hypotensive effect, irrespective of the initial blood pressure (P>0.10). When compared to placebo, the urinary output increased significantly with furosemide 12.5, 25, or 40 mg twice daily (P<0.05, P<0.01 and P<0.001, respectively) but not with the HCTZ group (P>0.10). Sodium level did not alter during the various treatment periods when compared with the placebo period, or between the individual treatment periods (P>0.10). Potassium level fell significantly during the HCTZ period (P<0.001) and furosemide 25 and 40 mg twice daily period (P<0.01 and P<0.001, respectively). Potassium level was not significantly affected with furosemide 12.5 mg twice daily (P>0.10).
Araoye et al.[35] (1978) HCTZ 50 mg BID vs furosemide 40 mg	DB, XO Patients with hypertension	N=not specified 3 months	Primary: Blood Pressure	Primary: Furosemide and HCTZ significantly reduced blood pressure. The decrease in blood pressure was consistently greater in the HCTZ group than with furosemide; however the difference was significant in regards to SBP only.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID				
Madkour et al.[36] (1996) HCTZ 50 mg QD vs indapamide 2.5 mg QD	RCT Patients aged 32 to 70 years with impaired renal function for 1 to 15 years and moderate hypertension for 2 to 27 years, initial creatinine clearance between 32 and 80 mL/min/1.73 m^2 body surface area	N=28 24 months	Primary: Blood pressure, changes in creatinine clearance	Primary: Blood pressure normalized in all patients taking either indapamide or HCTZ. There were no significant differences in SBP or DBP between groups. At 24 months, creatinine clearance progressively increased from 58±4.4 to 72±4.4 mL/min/1.73 m^2 body surface area in patients treated with indapamide (P<0.01). Creatinine clearance progressively decreased from 65±3.0 to 53±3.0 mL/min/1.73 m^2 body surface area in patients treated with HCTZ (P<0.01). Creatinine clearance significantly increased by 28.5±4.4% with indapamide and decreased by 17.4±3.0% with thiazide therapy (P<0.01).
Ames[37] (1996) HCTZ ≤25 mg (or its equivalent in other thiazides) up to 112.5 mg QD vs indapamide 2.5 mg QD	MA Patients with hypertension	N=1,547 (13 trials) 1 to 25 months	Primary: Comparison of the effects of thiazides and indapamide on blood lipids and blood pressure	Primary: The mean change from baseline was 1.4% for total cholesterol, 5.5% for high density lipoprotein cholesterol, and ─0.5% for triglycerides with indapamide. None of the differences were statistically significant. Low-dose thiazide therapy did not decrease total cholesterol at any data point. The mean percent increase in total cholesterol was 3.8%, in high density lipoprotein cholesterol was 3.1%, and in triglycerides was 10.8% with low-dose HCTZ. The increases in total cholesterol and triglycerides from baseline was statistically significant (P<0.01). The mean change in total cholesterol was 6.3%, in high density lipoprotein cholesterol was ─0.5%, and in triglycerides was 19.5% for higher doses of HCTZ. Increases from baseline in total cholesterol and triglycerides were statistically significant. SBP decreased more with higher doses of HCTZ than with low-dose thiazide therapy (P<0.05). The effects of indapamide on systolic arterial pressure were intermediate between, and not statistically different from, either thiazide dose. Decreases in DBP did not differ among groups.
Larochelle et al.[38]	DB, RCT	N=266	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1985) HCTZ 50 mg vs amiloride 5 mg and HCTZ 50 mg	Ambulant patients, 18 to 70 years of age with essential hypertension who after not being treated for at least 2 weeks prior to the study had a supine DBP of 95 to 109 mm Hg and a serum potassium level of >3.5 mmol/L	8 weeks	Blood pressure and serum potassium concentration	At 8 weeks, there were no statistically significant differences between groups in the mean blood pressure reductions. During the 8 weeks of treatment, the group receiving combination therapy experienced a decrease in the mean supine blood pressure and mean serum potassium level. Respectively these reductions were from 156/99 to 138/88 mm Hg and from 4.23 to 3.91 mmol/L. During the 8 weeks of treatment, the monotherapy group experienced a reduction in the mean supine blood pressure and mean serum potassium level; respectively from 157/99 to 138/87 mm Hg and from 4.16 to 3.69 mmol/L. Hypokalemia occurred less frequently in the combination group than in the monotherapy group (respectively, 14% and 29%; P=0.0026). However, the proportions of patients with a potassium level exceeding 4.5 mmol/L were similar 4.5% and 3.9%, respectively.
Salmela et al.[39] (1986) HCTZ 25 mg daily vs amiloride 2.5 mg and HCTZ 25 mg daily	DB, MC, PG, RCT Men and women with mild to moderate hypertension, mean 66.7 years of age	N=40 12 weeks	Primary: Changes in blood pressure	Primary: At the end of the first treatment period, mean supine SBP and DBP was 161 and 91 mm Hg for subjects receiving combination treatment; from baseline week 4; P<0.01 and P<0.001, respectively. At the end of the first treatment period, mean supine SBP and DBP was 165 and 96 mm Hg for subjects receiving HCTZ monotherapy; P<0.01, from baseline week 4 to the end of the first treatment period. At the end of the second treatment period, mean supine SBP and DBP was 154 and 86 mm Hg for subjects receiving combination treatment; from baseline week 4 to the end of the second treatment period; P<0.01 and P<0.001. At the end of the second treatment period, mean supine SBP and DBP was 155 and 90 mm Hg for subjects receiving HCTZ monotherapy; for both; P<0.001 from baseline week 4 to the end of the second treatment period. There were no statistically significant differences in blood pressure reduction between the 2 groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Multicenter Diuretic Cooperative Study Group[40] (1981) HCTZ 50 mg QD vs amiloride 5 mg and HCTZ 50 mg QD (combination entity) vs amiloride 5 mg QD	DB, MC, RCT Patients 21 to 69 years of age with mild to moderate essential hypertension (supine DBP 95 to 115 mm Hg)	N=179 12 weeks	Primary: Change from baseline in average supine SBP and DBP Secondary: Heart rate, body weight, serum potassium	Primary: Baseline vs 12-week average supine blood pressure was 153/101 vs 139/93 mm Hg for amiloride, 160/100 vs 137/90 mm Hg for amiloride-HCTZ, and 154/101 vs 134/89 mm Hg for HCTZ. Reductions in supine blood pressure was significant in all treatment groups (P<0.01). The SBP reduction was greater with amiloride-HCTZ than with amiloride at all weeks and HCTZ at 4 and 8 weeks (P<0.05, both). Secondary: No significant changes from baseline in heart rate were observed with amiloride or HCTZ. An increase in heart rate was observed with amiloride-HCTZ of 3.3 bpm (P<0.05). Changes in body weight from baseline were –1.17 kg for amiloride-HCTZ, –0.72 kg for HCTZ, and 0.045 kg for amiloride (P<0.05, for amiloride-HCTZ only). Changes in serum potassium from baseline were 0.23 mEq/L for amiloride (P<0.01), –0.38 mEq/L for amiloride-HCTZ (P<0.01), and –0.59 mEq/L for HCTZ (P<0.01). The HCTZ change was statistically greater than the amiloride-HCTZ change (P<0.05). Nearly 23% of HCTZ, 2% of amiloride-HCTZ, and 0% of amiloride patients experienced hypokalemia.
Johnson et al.[25] (2009) HCTZ 12.5-25 mg QD for 9 weeks, followed by HCTZ QD and atenolol 50-100 mg QD for 9 weeks vs atenolol 50-100 mg QD for 9 weeks, followed	RCT Patients 17 to 65 years of age mild to moderate essential hypertension	N=368 15-18 weeks	Primary: Blood pressure lowering effect of drug initiation order: the addition of a β-blocker to a thiazide versus the addition of a thiazide to a β-blocker	Primary: When analyzed by order of initiation of the two drugs, the response to HCTZ + atenolol was greater overall than that seen for atenolol + HCTZ (P=0.0007 and P<0.0001). This study suggests that initiation of HCTZ followed by atenolol results in greater BP lowering as compared with initiation in the reverse order, with differences that are potentially clinically important.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by atenolol QD and HCTZ 12.5-25 mg QD for 9 weeks				
Baguet et al.[30] (2007) HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, candesartan cilexetil*, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan, and aliskiren	MA Patients aged >18 years with mild or moderate essential hypertension (SBP blood pressure 140–179 mm Hg and/or DBP 90–109 mm Hg)	N=10,818 (80 trials) 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP	Primary: Diuretics (–19.2 mm Hg; 95% CI, –20.3 to –18.0), calcium-channel blockers (–16.4 mm Hg; 95% CI, –17.0 to –15.8) and angiotensin converting enzyme inhibitors (–15.6 mm Hg; 95% CI, –17.6 to –13.6) produced the greatest reductions in SBP from baseline. The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (–11.4 mm Hg; 95% CI, –12.0 to –10.9), calcium-channel blockers (–11.4 mm Hg; 95% CI, –11.8 to –11.1), and diuretics (–11.1 mm Hg; 95% CI, –11.7 to –10.5). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: –19.2 mm Hg (95% CI, –20.3 to –18.0) and –11.1 mm Hg (95% CI, –11.7 to –10.5), respectively. β-Blockers: –14.8 mm Hg (95% CI, –15.9 to –13.7) and –11.4 mm Hg (95% CI, –12.0 to –10.9), respectively. Calcium-channel blockers: –16.4 mm Hg (95% CI, –17.0 to –15.8) and –11.4 mm Hg (95% CI, –11.8 to –11.1), respectively. Angiotensin converting enzyme inhibitors: –15.6 mm Hg (95% CI, –17.6 to –13.6) and –10.8 mm Hg (95% CI, –11.9 to –9.7), respectively. Angiotensin II receptor antagonists: –13.2 mm Hg (95% CI, –13.6 to –12.9) and –10.3 mm Hg (95% CI, –10.5 to –10.1), respectively. Renin inhibitor: –13.5 mm Hg (95% CI, –14.2 to –12.9) and –11.3 mm Hg (95% CI, –11.7 to –10.9), respectively.

*Agent not available in the United States (US)
Drug regimen abbreviations: BID=twice daily, KCL=potassium chloride, QAM=every morning, QD=once daily,
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single blind, SR=sustained release, XO=crossover
Other abbreviations: β-blockers=β-adrenergic blocking agents, bpm=beats per minute, CCBs=calcium-channel blocking agents, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, NYHA=New York Heat Association, SBP=systolic blood pressure

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 Thiazide Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Chlorothiazide	injection, suspension, tablet	Diuril®, Diuril Sodium®*	$	$
Hydrochlorothiazide	capsule, tablet	Microzide®*	$	$
Methyclothiazide	tablet	N/A	N/A	$

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

X. Conclusions

The thiazide diuretics are approved for the treatment of hypertension and edema due to renal dysfunction.[1-9] They are also approved as adjunctive therapy for the management of edema associated with congestive heart failure, hepatic cirrhosis, as well as corticosteroid and estrogen therapy. All of the agents are available in a generic formulation.

Guidelines recommend the use of diuretics and sodium restriction for the management of ascites due to cirrhosis.[41-42] Spironolactone is recommended as first-line therapy, either as monotherapy or in combination with furosemide. Amiloride is an alternative treatment option in patients experiencing gynecomastia with spironolactone. Triamterene, metolazone and hydrochlorothiazide have also been used to treat ascites.

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload.[13,15-16] Loop diuretics are generally recommended as initial therapy in patients with left ventricular dysfunction.[15-16] For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[13,15]

There are several national and international organizations that have published guidelines on the treatment of hypertension.[14,17-20,22-24] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension, either as monotherapy or in combination with other agents.[14,17,20,24] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[18-19] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[18-19] Guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[14,17-20,22-24] Most patients will need more than one antihypertensive medication to achieve blood pressure goals. In clinical trials, the thiazide diuretics have been shown to effectively lower blood pressure.[25-40] There were no studies found in the medical literature that directly compared the efficacy and safety of the thiazide diuretics for the treatment of hypertension.

There is insufficient evidence to support that one brand thiazide diuretic 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 thiazide diuretics 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 thiazide diuretic 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 Thiazide-Like Diuretics
AHFS Class 402824
November 10, 2010

I. Overview

The thiazide-like diuretics are approved for the treatment of edema and hypertension.[1-8] They inhibit sodium reabsorption in the distal convoluted tubule of the nephron. This results in an initial modest reduction in plasma volume and cardiac output.[9] However, long-term maintenance of decreased blood pressure has been shown to be associated with partial reversal of the hemodynamic changes as plasma volume and cardiac output return to baseline.[9] Although thiazide-like diuretics are pharmacologically similar to thiazide diuretics, there are chemical differences in the molecular structure that differentiate these agents. Indapamide may produce an independent vascular action, which results in a reduction in total peripheral resistance.[1-3] Metolazone may produce diuresis in patients with glomerular filtration rates below 20 mL/minute.[8]

The thiazide-like diuretics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the agents are available in a generic formulation. This class was last reviewed in September 2008.

Table 1. Thiazide-Like Diuretics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chlorthalidone	tablet*	Thalitone®	chlorthalidone
Indapamide	tablet	N/A	indapamide
Metolazone	tablet	Zaroxolyn®*	metolazone

*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 thiazide-like diuretics are summarized in Table 2. For a comprehensive overview of the pharmacologic management of heart failure and hypertension, please refer to the Appendix.

Table 2. Treatment Guidelines Using the Thiazide-Like Diuretics

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases (AASLD): **Management of Adult Patients with Ascites Due to Cirrhosis: An Update[40] (2009)**	• First-line treatment of patients with cirrhosis and ascites consists of sodium restriction and diuretics (oral spironolactone with or without oral furosemide). • In patients experiencing painful gynecomastia with spironolactone, amiloride may be an appropriate substitute. • Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites. Hydrochlorothiazide can also cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide. • An initial therapeutic abdominal paracentesis should be performed in patients with tense ascites. Sodium restriction and oral diuretics should then be initiated. • Diuretic-sensitive patients should preferably be treated with sodium restriction and oral diuretics rather than with serial paracenteses.
World Gastroenterology Organization (WGO) Practice	• Initial oral diuretic therapy consists of single daily doses of spironolactone or spironolactone in addition to furosemide.

Clinical Guideline	Recommendation(s)
Guideline: **Management of Ascites Complicating Cirrhosis in Adults**[41]	• Spironolactone monotherapy is more effective compared to furosemide monotherapy. However its use should be restricted to patients exhibiting minimal fluid overload. • Spironolactone monotherapy may be complicated by hyperkalemia and gynecomastia. Amiloride and triamterene are substitutes for spironolactone. • Indications of diuretic resistance include minimal to no weight loss and urinary sodium excretion of <78 mmol/day. Diuretic therapy should be discontinued in patients who develop encephalopathy, clinically significant complications of diuretics, hyperkalemia, metabolic acidosis with spironolactone, and whose serum sodium is <120 mmol/L or serum creatinine >2 mg/dL.
Heart Failure Society of America (HFSA): **2010 Comprehensive Heart Failure Practice Guideline**[14] **(2010)**	<u>Patients With Left Ventricular Systolic Dysfunction</u> • Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. • Torsemide may be considered in patients in whom erratic diuretic effect or absorption is present, particularly those with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. • The addition of metolazone or chlorothiazide to loop diuretics should be considered in patients with persistent fluid retention despite high-dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion. • Patients requiring diuretic therapy to treat fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. <u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u> • Diuretic treatment is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. <u>Patients With Acute Decompensated Heart Failure (ADHF)</u> • It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally. • Intravenous vasodilators and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. <u>Patients With Heart Failure and Hypertension</u> • The use of an ACE inhibitor is recommended. • The addition of a β-blocker is recommended even if blood pressure is controlled. • If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine CCB (e.g., amlodipine or felodipine) or other antihypertensive drugs.
American College of Cardiology Foundation (ACCF)/American	<u>Patients at Risk for Developing Heart Failure (Stage A)</u> • Systolic and diastolic hypertension should be controlled according to

Clinical Guideline	Recommendation(s)
Heart Association (AHA): **2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults[12] (2009)**	contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy. Patients With Current or Prior Symptoms of Heart Failure (Stage C) • Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention. Patients With Heart Failure and Normal Left Ventricular Ejection Fraction • Diuretics are recommended to control pulmonary congestion and peripheral edema. Patients With Refractory End-Stage Heart Failure (Stage D) • Treatment of fluid retention is important. Hospitalized Patients • For patients admitted with heart failure who have evidence of significant fluid overload, intravenous loop diuretics should be started as soon as possible in the emergency department. If patients are already receiving loop diuretics, the initial intravenous dose should equal or exceed their chronic daily oral dose. • When diuresis is inadequate to relieve congestion, the diuretic regimen should be intensified using either a higher dose of loop diuretic, addition of a second diuretic, or continuous infusion of a loop diuretic.
European Society of Cardiology (ESC): **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[15] (2008)**	Pharmacologic Therapy of Chronic Heart Failure • Diuretics are recommended in patients with heart failure and clinical signs or symptoms of congestion. • Diuretics cause activation of the renin–angiotensin–aldosterone system in patients with mild symptoms of heart failure and should usually be used in combination with an ACE inhibitor or ARB. • In general, a loop diuretic will be required in moderate or severe heart failure. A thiazide may be used in combination with loop diuretics for resistant edema, but with caution to avoid dehydration, hypovolemia, hyponatremia, or hypokalemia. Management of Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (HFPEF) • Diuretics are used to control sodium and water retention and relieve shortness of breath and edema.
European Society of Hypertension (ESH): **Reappraisal of European Guidelines on Hypertension Management[18] (2009)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. • Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided. • In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs. • The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of

Clinical Guideline	Recommendation(s)
	efficacy. • Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance. • When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic. • Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly. • All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
European Society of Hypertension (ESH)/European Society of Cardiology (ESC): **Guidelines for the Management of Hypertension[17] (2007)**	• The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, nondihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics). • Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.
National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): **Hypertension: Management in Adults in Primary Care: Pharmacological Update[19] (2006)**	• Initial therapy in patients ≥55 years of age should be a CCB or a thiazide diuretic. • If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added. • If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker. • If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
National Heart, Lung, and Blood Institute (NHLBI): **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood**	• Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes. • High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-

Clinical Guideline	Recommendation(s)
Pressure (JNC 7)[13] (2004)	blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor). • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs, and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2-4 times higher in African American patients. • Thiazide diuretics are useful in slowing demineralization in osteoporosis. • Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): **K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[23] (2004)**	• Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, nondihydropyridine CCBs). • Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB. • Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals. • Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.
World Health Organization (WHO)/International Society of Hypertension (ISH): **2003 WHO/ISH Statement on Management of Hypertension[16] (2003)**	• A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class. • If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents. • When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients.

Clinical Guideline	Recommendation(s)
	• Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).
International Society on Hypertension in Blacks: **Management of High Blood Pressure in African Americans**[22] **(2003)**	• CCBs and thiazide diuretics may be more effective than other drug classes in African Americans. • Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes**[21] **(2010)**	• The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are needed, a thiazide diuretic may be added if estimated glomerular filtration rate (GFR) is ≥30 ml/min/1.73 m^2 or a loop diuretic for patients whose estimated GFR is <30 ml/min/1.73 m^2. • Multiple drug therapy is generally required to achieve blood pressure goals.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the thiazide-like diuretics 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 Thiazide-Like Diuretics[1-8]

Indication	Chlorthalidone	Indapamide	Metolazone
Edema			
Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy	✔		
Treatment of edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure	✔		
Salt and fluid retention associated with congestive heart failure		✔	
Salt and water retention, including edema accompanying congestive heart failure			✔
Salt and water retention, including edema accompanying renal disease, including the nephrotic syndrome and states of diminished renal function			✔
Hypertension			
Treatment of hypertension	✔ *	✔ *	✔ *

*Alone or in combination with other antihypertensive agents.

IV. Pharmacokinetics

The pharmacokinetic parameters of the thiazide-like diuretics are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Thiazide-Like Diuretics[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Chlorthalidone	65	75	Not reported	Renal (50-74)	40-89
Indapamide	100	71-79	Liver, extensive	Renal (60-70) Bile (23) Feces (16-20)	14-15
Metolazone	40-65	95	Not reported	Renal (56)	8-14

V. Drug Interactions

Significant drug interactions with the thiazide-like diuretics are listed in Table 5.

Table 5. Significant Drug Interactions with the Thiazide-Like Diuretics[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	1	Lithium	Thiazide-like diuretics may decrease the renal excretion of lithium and produce elevated serum lithium concentrations with toxicity.
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	2	Diazoxide	The pharmacologic effects of thiazide-like drugs and diazoxide may be increased. Hyperglycemia, hyperuricemia and hypotension may occur.
Thiazide-like diuretics (chlorthalidone, indapamide, metolazone)	2	Digitalis glycosides	Excretion of potassium and magnesium is increased by thiazide-like diuretics. Potassium and magnesium depletion can sensitize the myocardium to the toxic effects of digitalis glycosides.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the thiazide-like diuretics are listed in Table 6. The boxed warning for metolazone is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Thiazide-Like Diuretics[1-8]

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Cardiovascular			
Chest pain	-	<5	✔
Irregular heartbeat	-	<5	-
Orthostatic hypotension	✔	<5	✔
Palpitations	-	<5	✔
Peripheral edema	-	<5	-
Premature ventricular contractions	-	<5	-

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Venous thrombosis	-	-	✔
Volume depletion	-	-	✔
Central Nervous System			
Anxiety	-	≥5	-
Blurred vision	-	<5	✔
Depression	-	<5	-
Dizziness	✔	≥5	✔
Drowsiness	-	<5	✔
Fatigue	-	≥5	✔
Headache	✔	≥5	✔
Insomnia	-	<5	-
Lethargy	-	≥5	-
Lightheadedness	-	<5	✔
Nervousness	-	<5	-
Neuropathy	-	-	✔
Paresthesia	✔	<5	✔
Restlessness	✔	-	✔
Syncope	-	-	✔
Tension	-	≥5	-
Vertigo	✔	<5	✔
Weakness	✔	≥5	✔
Xanthopsia	✔	-	-
Dermatological			
Dermatitis	-	-	✔
Petechiae	-	-	✔
Photosensitivity	✔	-	✔
Pruritus	-	<5	✔
Purpura	✔	-	✔
Rash	✔	<5	✔
Skin necrosis	-	-	✔
Stevens-Johnson syndrome	-	-	✔
Toxic epidermal necrolysis	✔	✔	✔
Urticaria	✔	<5	✔
Gastrointestinal			
Abdominal pain	-	<5	✔
Anorexia	✔	<5	✔
Constipation	✔	<5	✔
Cramping	✔	-	-
Diarrhea	✔	<5	✔
Dry mouth	-	<5	✔
Dyspepsia	-	<5	-
Epigastric distress	-	-	✔
Gastric irritation	✔	<5	-
Nausea	✔	<5	✔
Pancreatitis	✔	-	✔
Vomiting	✔	<5	✔
Genitourinary			
Impotence	✔	<5	✔
Nocturia	-	<5	✔
Polyuria	-	<5	-
Hematologic			
Agranulocytosis	✔	-	✔
Aplastic anemia	✔	-	✔
Leukopenia	✔	-	✔

Adverse Event(s)	Chlorthalidone	Indapamide	Metolazone
Thrombocytopenia	✔	-	✔
Laboratory Test Abnormalities			
Blood urea nitrogen increased	-	<5	✔
Hypercalcemia	✔	✔	✔
Hyperglycemia	✔	<5	✔
Hyperlipidemia	✔	-	-
Hyperuricemia	✔	<5	✔
Hypochloremia	-	<5	✔
Hypokalemia	✔	3-7	✔
Hypomagnesemia	✔	✔	✔
Hyponatremia	✔	<5	-
Hypophosphatemia	-	-	✔
Serum creatinine increased	-	-	✔
Musculoskeletal			
Asthenia	-	<5	-
Back pain	-	≥5	-
Joint pain	-	-	✔
Hypertonia	-	<5	-
Muscle spasm	✔	≥5	✔
Renal			
Glycosuria	✔	<5	✔
Respiratory			
Cough	-	<5	-
Pharyngitis	-	<5	-
Rhinitis	-	≥5	-
Sinusitis	-	<5	-
Other			
Chills	-	-	✔
Conjunctivitis	-	<5	-
Gout	-	-	✔
Hemoconcentration	-	-	✔
Hepatitis	-	-	✔
Infection	-	≥5	-
Jaundice	✔	-	✔
Necrotizing angiitis/vasculitis	-	-	✔
Vasculitis	✔	<5	-
Weight loss	-	<5	-

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for Metolazone[1]

WARNING
Do not interchange: Do not interchange Zaroxolyn® tablets and other formulations of metolazone that share its slow and incomplete bioavailability.

VII. Dosing and Administration

The usual dosing regimens for the thiazide-like diuretics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Thiazide-Like Diuretics[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chlorthalidone	Edema: Initial: 30 to 60 mg/day or 60 mg on alternate days; maintenance, 90 to 120 mg on alternate days or 120 mg/day Hypertension: Initial: 15 to 30 mg/day; maintenance, 45 to 50 mg/day	Safety and efficacy in children have not been established.	Tablet: 15 mg 25 mg 50 mg 100 mg
Indapamide	Edema: Initial: 2.5 mg/day; maintenance, 2.5 to 5 mg/day Hypertension: Initial: 1.25 mg/day; maintenance, 2.5 to 5 mg/day	Safety and efficacy in children have not been established.	Tablet: 1.25 mg 2.5 mg
Metolazone	Edema: 5 to 20 mg/day Hypertension: Initial: 2.5 to 5 mg/day, maintenance, 5 to 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5 mg 5 mg 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazide-like diuretics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Thiazide-Like Diuretics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypertension				
SHEP Cooperative Research Group[24] and Kostis et al.[25] (1991 and 1995) SHEP Chlorthalidone 12.5 mg QD vs placebo Dosage was doubled for patients failing to achieve SBP goals. If SBP goal was not reached with chlorthalidone 25 mg QD, atenolol 25 mg QD or matching placebo was added to the drug regimen. Reserpine 0.05 mg QD or matching placebo was substituted in patients with	DB, MC, PC, RCT Patients aged ≥60 years with SBP between 160 and 219 mm Hg and DBP <90 mm Hg	N=4,736 Mean 4.5 years	Primary: Total stroke Secondary: Sudden or rapid cardiac death (defined as death within 1 hour or within 1 to 24 hours of the onset of severe cardiac symptoms), nonfatal or fatal myocardial infarction, other cardiovascular death, transient ischemic attack	Primary: With a mean follow-up of 4.5 years, the stroke occurred in 103 patients in the active treatment group compared to 159 patients in the placebo group (RR, 0.64; 95% CI, 0.5 to 0.82; P=0.0003). Stroke incidence was lower in patients taking active treatment compared to placebo in all baseline age groups: 60 to 69 years (34 vs 47 events, respectively), 70 to 79 years (48 vs 74 events, respectively), 80+ years (21 vs 38 events, respectively). The results were stratified according to whether patients had had previous antihypertensive therapy or not. In both stratified groups, there was a decrease in the risk of stroke with active treatment compared to placebo. For patients who were not receiving antihypertensive medication at initial contact, the RR, of stroke was 0.69 (95% CI, 0.51 to 0.95; P=0.02). For patients who had been receiving antihypertensive medication at initial contact, the RR, of stroke was 0.57 (95% CI, 0.38 to 0.85; P=0.01). Secondary: There were 23 sudden and 21 rapid deaths in the active treatment group compared to 23 sudden and 24 rapid deaths in the placebo group (RR, 10; 95% CI, 0.56 to 1.78 vs RR, 0.87; 95% CI, 0.48 to 1.56, respectively). There were 50 nonfatal and 15 fatal myocardial infarctions in the active treatment group compared to 74 nonfatal and 26 fatal myocardial infarctions in the placebo group (RR, 0.67; 95% CI, 0.47 to 0.96 vs RR, 0.57; 95% CI, 0.30 to 18, respectively. There were 21 other cardiovascular deaths in the active treatment group compared to 25 in the placebo group (RR, 0.87; 95% CI, 0.49 to 1.55).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
contraindications to atenolol.				There were 62 transient ischemic attacks in the active treatment group compared to 82 in the placebo group (RR, 0.75; 95% CI, 0.54 to 14). In the combined endpoints, the RR, of nonfatal myocardial infarction or coronary heart disease death was 0.73 (95% CI, 0.57 to 0.94), coronary heart disease was 0.75 (95% CI, 0.60 to 0.94), cardiovascular disease was 0.68 (95% CI, 0.58 to 0.79). The RR, for atenolol were 0.84 (95% CI, 0.54 to 1.30) for death, 1.34 (95% CI, 0.80 to 2.28) for stroke, and 17 (95% CI, 0.71 to 1.61) for cardiovascular disease. The RR, for reserpine were 0.65 (95% CI, 0.26 to 1.59) for death, 0.27 (95% CI, 0.04 to 2.26) for stroke, and 0.55 (95% CI, 0.20 to 1.49) for cardiovascular disease.
ALLHAT Collaborative Research Group[35] (2000) ALLHAT Chlorthalidone 12.5 to 25 mg QD vs doxazosin 2 to 8 mg QD	AC, DB, MC, RCT Patients aged 55 years or older who had stage 1 or stage 2 hypertension with ≥1 additional risk factor for coronary heart disease events (including previous myocardial infarction or stroke >6 months ago, left ventricular hypertrophy or echocardiography, history of type 2 diabetes, current cigarette smoking, high density lipoprotein	N=24,335 Median 3.3 years	Primary: Fatal coronary heart disease or nonfatal myocardial infarction combined Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease, cancer, end-stage renal disease	Primary: There was no significant difference in the primary outcome between doxazosin and chlorthalidone treatments (risk ratio 13; 95% CI, 0.90 to 1.17; P=0.71). Secondary: Total mortality did not differ between the doxazosin and chlorthalidone treatments (4-year rates, 9.62% and 9.08%, respectively; RR 13; 95% CI, 0.90-1.15;P=0.56). The doxazosin group, compared with the chlorthalidone group, had a higher risk of stroke (RR 1.19; 95% CI, 11-1.40; P=0.04) and combined CVD (4-year rates 25.45% vs 21.76%; RR 1.25; 95% CI, 1.17-1.33; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	cholesterol <35 mg/dL, or documentation of other atherosclerotic cardiovascular disease)			
ALLHAT Collaborative Research Group[36] (2002) ALLHAT Chlorthalidone 12.5 to 25 mg/day vs amlodipine 2.5 to 10 mg/day vs lisinopril 10 to 40 mg/day	AC, DB, MC, RCT Patients aged 55 years or older who had stage 1 or stage 2 hypertension with ≥1 additional risk factor for coronary heart disease events (including previous myocardial infarction or stroke >6 months ago, left ventricular hypertrophy or echocardiography, history of type 2 diabetes, current cigarette smoking, high density lipoprotein cholesterol <35 mg/dL, or documentation of other atherosclerotic cardiovascular disease)	N=33,357 4 to 8 years (mean 4.9 years)	Primary: Fatal coronary heart disease or nonfatal myocardial infarction combined Secondary: All cause mortality, fatal and nonfatal stroke, combined coronary heart disease, combined cardiovascular disease, cancer, end-stage renal disease	Primary: There was no significant difference in the primary outcome between amlodipine and chlorthalidone treatments, or between lisinopril and chlorthalidone (risk ratio 0.98; 95% CI, 0.90 to 17; P=0.65 and risk ratio 0.99; 95% CI, 0.91 to 18; P=0.81). Secondary: The secondary endpoints did not differ between amlodipine and chlorthalidone for all-cause mortality, combined coronary heart disease, stroke, combined cardiovascular disease, angina, coronary revascularization, peripheral arterial disease, cancer, or end-stage renal disease. However, heart failure and hospitalized/fatal heart failure, components of combined cardiovascular disease, occurred at higher rates with amlodipine than with chlorthalidone (risk ratio 1.38; 95% CI, 1.25 to 1.52; P<0.001 and risk ratio 1.35; 95% CI, 1.21 to 1.50; P<0.001, respectively). In a comparison of lisinopril to chlorthalidone, the secondary endpoints of all-cause mortality, combined coronary heart disease, peripheral arterial disease, cancer, or end-stage renal disease did not significantly differ between treatment groups. However, there were higher rates of stroke (risk ratio 1.15; 95% CI, 12 to 1.30; P=0.02), combined cardiovascular disease (risk ratio 1.10; 95% CI, 15 to 1.16; P<0.001), heart failure (risk ratio 1.19; 95% CI, 17 to 1.31; P<0.001), angina (hospitalized or treated [risk ratio 1.11; 95% CI, 13 to 1.20; P=0.01]), and coronary revascularizations (risk ratio 1.10; 95% CI, 10 to 1.21; P=0.05) observed in the lisinopril group compared to the chlorthalidone group.
Pupita et al.[28] (1983)	RCT, SC, XO	N=36	Primary: Blood pressure	Primary: Patients taking chlorthalidone had significantly lower SBP at each

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chlorthalidone 50 mg QD vs furosemide 25 mg QD	Men and women with a mean age of 53.9±9.2 years with mild to moderate hypertension	12 months	Secondary: Plasma electrolytes, adverse events	monthly measurement compared to baseline (P<0.01). However, only DBP values at month 5 were significant compared to baseline (P<0.05). Patients taking furosemide had significantly lower SBP at months 3, 4, and 5 compared to baseline (P<0.05 for month 3, and P<0.01 for months 4 and 5). DBP values were significantly lower at all monthly measurements compared to baseline in patients taking furosemide (P<0.01). At month 1, SBP decreased by 19.4 mm Hg with chlorthalidone and by 21.2 mm Hg with furosemide (P<0.001). DBP decreased by 11 mm Hg with chlorthalidone and by 12.6 mm Hg with furosemide at month 1 (P<0.001). Secondary: There were no significant changes in serum sodium levels with either chlorthalidone or furosemide. Patients taking chlorthalidone had significantly lower serum chloride levels compared to baseline at all points (P<0.01), whereas patients taking furosemide had significantly lower levels only at month 6 (P<0.05). Both chlorthalidone and furosemide significantly reduced serum potassium levels at all points compared to baseline (P<0.01). Patient taking chlorthalidone reported adverse effects including dizziness, transient abdominal disorder, and slight weakness. Patients taking furosemide reported transient early weakness and irritability. The rate of adverse events was not statistically significant in either treatment group.
Ernst et al.[29] (2006) Chlorthalidone 12.5 mg QAM vs HCTZ 25 mg QAM	RCT, SB, XO Men and women aged 18 to 79 years with prehypertension or a new or established diagnosis of hypertension (stage 1 or 2), not receiving	N=30 8 weeks plus 4 week washout period	Primary: Comparison of the change in 24-hour mean SBP and DBP from baseline to week 8 Secondary: Comparison of changes in mean SBP and mean	Primary: At week 8, there was a greater reduction in 24-hour mean SBP with chlorthalidone 25 mg/day compared to HCTZ 50 mg/day compared to baseline (−12.4±1.8 vs −7.4±1.7 mm Hg, respectively; P=0.054). Secondary: There was a trend in favor of greater reduction in SBP with chlorthalidone than with HCTZ at each office visit. However, the difference was only statistically significant at week 2 (−15.7±2.2 vs −4.5±2.1 mm Hg, respectively; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
At week 4, both HCTZ and chlorthalidone were titrated to 50 mg QAM and 25 mg QAM, respectively for the remainder of the study.	antihypertensive medications, and had an average office blood pressure value in the last 6 months between 140 and 179 mm Hg systolic or 90 and 109 mm Hg diastolic		DBP for office blood pressure at each visit, change in ambulatory daytime and nighttime mean SBP and DBP from baseline to week 8, development of hypokalemia	Although mean reductions in DBP was also greater with chlorthalidone compared to HCTZ at each study visit, the differences were not statistically significant at any visit (P>0.89 for all). The reduction in SBP during nighttime hours was −13.5±1.9 mm Hg for chlorthalidone and −6.4±1.7 mm Hg for HCTZ (P=0.009). The reduction in daytime mean SBP between both groups was not significantly different (−11.4±2.0 vs −8.1±1.9 mm Hg, respectively; P=0.230). Changes in serum potassium were similar between treatment groups (P=0.76). The incidence of hypokalemia was 50% in patients taking HCTZ and 46% in patients taking chlorthalidone (P=0.682).
Carter et al.[30] (2004) Chlorthalidone 12.5 to 600 mg/day vs HCTZ 12.5 to 450 mg/day	MA Included studies which evaluate the pharmacokinetic and blood pressure lowering effects of chlorthalidone and HCTZ	N=200 Duration varied per study	Primary: Blood pressure Secondary: Serum potassium	Primary: In a dose equivalence study comparing HCTZ 100 mg QD to chlorthalidone 50 mg QD, blood pressure (SBP/DBP) reduced by 18/8 and 25/10 mm Hg compared to baseline, respectively. In another study comparing HCTZ 25 mg and triamterene 50 mg QD, HCTZ 50 mg and triamterene 100 mg QD, and chlorthalidone 50 mg QD, the blood pressure reduction was 15/8, 18/12, and 25/16 mm Hg, respectively. One other dose equivalence study comparing HCTZ 50 mg BID and chlorthalidone 50 mg QD, blood pressure reduction was 22/16 and 18/15 mm Hg, respectively. All available studies were inspected and it was concluded that HCTZ 50 mg is approximately equivalent to chlorthalidone 25 to 37 mg. Furthermore, it was suggested that chlorthalidone doses should generally be approximately 50% to 75% of the typical HCTZ dose. Secondary: In a study comparing HCTZ 100 mg QD and chlorthalidone 50 mg QD, potassium increased slightly with chlorthalidone (0.02 mEq/L) and decreased significantly with HCTZ (0.22 mEq/L; P=0.009). However, in another study comparing HCTZ 50 mg BID and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				chlorthalidone 50 mg QD, serum potassium decreased by 0.38 mEq/L with HCTZ and by 0.03 mEq/L with chlorthalidone. The difference was not statistically significant (P<0.07).
Karotsis et al.[37] (2006) Chlorthalidone 12.5 mg QD plus diltiazem 240 mg QD vs felodipine 5 mg QD plus diltiazem 240 mg QD vs lisinopril 10 mg QD plus diltiazem 240 mg QD vs valsartan 80 mg QD plus diltiazem 240 mg QD	RCT Patients aged 25 to 79 years with uncontrolled hypertension (defined as average office blood pressure greater than 140/90 mm Hg for all or 153/85 mm Hg for diabetics or subjects under the age of 65, confirmed on 2 office visits at least 1 week apart) after at least 4 weeks of open monotherapy with diltiazem at 240 mg QD	N=211 8 weeks	Primary: Blood pressure	Primary: There was a significant decline in both office and home SBP and DBP during the study period for all treatment groups. The antihypertensive effect was more pronounced and reached statistical significance when home blood pressure monitoring was used in comparison to office blood pressure without the white-coat effect (P<0.001 for all blood pressure changes). With or without the white-coat effect, blood pressure still declined and the differences were statistically significant (P<0.0001 for all blood pressure changes).
Beckett et al.[42] (2008) HYVET Indapamide 1.5 mg/day vs	DB, MC, PC, RCT Patients ≥80 years (mean age 84 years) with sustained SBP ≥160 mm Hg	N=3,845 1.8 years (mean)	Primary: Fatal or nonfatal stroke Secondary: Death from any cause, death from cardiovascular causes, death from	Primary: At 2 years, 73.4% of patients in the active-treatment groups were receiving indapamide plus perindopril. Mean blood pressure while sitting was 15.0/6.1 mm Hg lower with active-treatment than placebo. Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, –1 to 51; P=0.06). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Perindopril 2 to 4 mg/day or matching placebo was added if necessary to achieve the target blood pressure of 150/80 mm Hg.			stroke	Active treatment was associated with a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P=0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, –1 to 40; P=0.06) and a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P=0.05). Active treatment was associated with a 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001). Fewer serious adverse events were reported in the active-treatment group (358 vs 448; P=0.001).
Milia et al.[31] (2006) Indapamide 2.5 mg QD vs bendro-flumethiazide* 2.5 mg QD	DB, PG, PRO, RCT Ambulant patients with a first-ever minor hemispheric ischemic stroke or transient ischemic attack	N=26 28 days	Primary: Blood pressure, cerebral blood flow	Primary: Both indapamide and bendroflumethiazide significantly reduced blood pressure from baseline (─14.7±12.5 mm Hg and ─7.7±9.16 mm Hg, respectively; P<0.001 and P=0.02, respectively). A nonsignificant trend toward greater blood pressure reduction was seen in patients taking indapamide. There were no statistically significant differences in blood pressure reduction between both treatment groups. There was a nonsignificant trend toward increases in blood flow in both treatment groups. However, there was no statistically significant differences in carotid blood flow between both treatment groups (P=0.04 for between-group comparison).
Madkour et al.[32] (1996) Indapamide 2.5 mg QD vs HCTZ 50 mg QD	RCT Patients aged 32 to 70 years with impaired renal function for 1 to 15 years and moderate hypertension for 2 to 27 years, initial creatinine clearance between 32 and 80 mL/min/1.73 m^2 body surface area	N=28 24 months	Primary: Blood pressure, changes in creatinine clearance	Primary: Blood pressure normalized in all patients taking either indapamide or HCTZ. There were no significant differences in SBP or DBP between groups. At 24 months, creatinine clearance progressively increased from 58±4.4 to 72±4.4 mL/min/1.73 m^2 body surface area in patients treated with indapamide (P<0.01). Creatinine clearance progressively decreased from 65±3.0 to 53±3.0 mL/min/1.73 m^2 body surface area in patients treated with HCTZ (P<0.01). Creatinine clearance significantly increased by 28.5±4.4% with indapamide and decreased by 17.4±3.0% with thiazide therapy (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Akram et al.[26] (2007) NATIVE Indapamide SR 1.5 mg QD added to background antihypertensive therapy	OL Patients remaining hypertensive (145-180/95-105 mm Hg) while receiving an ACE inhibitor, β-blocker, calcium-channel blocker, angiotensin II receptor blocker, α-blocker, or other therapy	N=1,941 3 months	Primary: Blood pressure Secondary: Glucose and cholesterol levels	Primary: At 3 months, SBP and DBP both decreased significantly compared to baseline. SBP had a change from 166±16 mm Hg at baseline to 132±12 mm Hg at 3 months. DBP had a change from 102±8 mm Hg at baseline to 83±6 mm Hg at 3 months (P<0.0001 for both). At study end, 84% of patients achieved target SBP of ≤140 mm Hg and 61% achieved blood pressure normalization (SBP/DBP <140/90 mm Hg). Secondary: Glucose and cholesterol levels were unaffected by indapamide SR.
Hua et al.[34] (1976) Metolazone 5 mg QD vs chlorothiazide up to 5 g BID	XO Patients with hypertension	N=20 Duration not specified	Primary: Blood pressure, serum potassium	Primary: Blood pressures on metolazone tended to be lower than on chlorothiazide, but the difference was not statistically significant. Both agents significantly lowered serum potassium concentrations and total body potassium to a similar degree. However, the serum potassium did not fall below the normal range in any patient and no potassium supplements were required.
ADVANCE Collaborative Group[38] (2007) Perindopril (2 to 4 mg) and indapamide (0.625 to 1.25 mg) QD vs placebo	PC, DB, MC, RCT Adults 55 years of age or older who were diagnosed with type 2 diabetes at age 30 or older. Eligible patients also had a history of CVD or at least one other risk factor for CVD.	N=11,140 Mean 4.3 years	Primary: Composites of major macrovascular and microvascular events (death from cardiovascular disease, nonfatal stroke, nonfatal myocardial infarction, or new renal or diabetic eye disease)	Primary: The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs 938 [16.8%] placebo; hazard ratio 0.91, 95% CI 0.83-10, p=0.04). Secondary: The relative risk of death from cardiovascular disease was reduced by 18% (211 [3.8%] active vs 257 [4.6%] placebo; 0.82, 0.68-0.98, p=0.03) and death from any cause was reduced by 14% (408 [7.3%] active vs 471 [8.5%] placebo; 0.86, 0.75-0.98, p=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Macrovascular and microvascular endpoints analyzed separately	
Ames[33] (1996) Indapamide 2.5 mg QD vs HCTZ ≤25 mg or its equivalent in other thiazides, up to 112.5 mg QD	MA Patients with hypertension	N=1,547 (13 trials) 1 to 25 months	Primary: Comparison of the effects of thiazides and indapamide on blood lipids and blood pressure	Primary: The mean change from baseline was 1.4% for total cholesterol, 5.5% for high density lipoprotein cholesterol, and ─0.5% for triglycerides with indapamide. None of the differences were statistically significant. Low-dose thiazide therapy did not decrease total cholesterol at any data point. The mean percent increase in total cholesterol was 3.8%, in high density lipoprotein cholesterol was 3.1%, and in triglycerides was 10.8% with low-dose HCTZ. The increases in total cholesterol and triglycerides from baseline was statistically significant (P<0.01). The mean change in total cholesterol was 6.3%, in high density lipoprotein cholesterol was ─0.5%, and in triglycerides was 19.5% for higher doses of HCTZ. Increases from baseline in total cholesterol and triglycerides were statistically significant. SBP decreased more with higher doses of HCTZ than with low-dose thiazide therapy (P<0.05). The effects of indapamide on systolic arterial pressure were intermediate between, and not statistically different from, either thiazide dose. Decreases in DBP did not differ among groups.
Baguet et al.[27] (2007) Indapamide SR*, HCTZ, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, candesartan	MA Patients aged >18 years with mild or moderate essential hypertension (SBP blood pressure 140–179 mm Hg and/or DBP 90–109 mm Hg)	N=10,818 (80 trials) 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (–19.2 mm Hg; 95% CI, –20.3 to –18.0), calcium-channel blockers (–16.4 mm Hg; 95% CI, –17.0 to –15.8) and angiotensin converting enzyme inhibitors (–15.6 mm Hg; 95% CI, –17.6 to –13.6) produced the greatest reductions in SBP from baseline. The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (–11.4 mm Hg; 95% CI, –12.0 to –10.9), calcium-channel blockers (–11.4 mm Hg; 95% CI, –11.8 to –11.1),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cilexetil*, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan, and aliskiren				and diuretics (–11.1 mm Hg; 95% CI, –11.7 to –10.5). The weighted average reduction of SBP and DBP for each drug class were as follows: Diuretics: –19.2 mm Hg (95% CI, –20.3 to –18.0) and –11.1 mm Hg (95% CI, –11.7 to –10.5), respectively. β-Blockers: –14.8 mm Hg (95% CI, –15.9 to –13.7) and –11.4 mm Hg (95% CI, –12.0 to –10.9), respectively. Calcium-channel blockers: –16.4 mm Hg (95% CI, –17.0 to –15.8) and –11.4 mm Hg (95% CI, –11.8 to –11.1), respectively. Angiotensin converting enzyme inhibitors: –15.6 mm Hg (95% CI, –17.6 to –13.6) and –10.8 mm Hg (95% CI, –11.9 to –9.7), respectively. Angiotensin II receptor antagonists: –13.2 mm Hg (95% CI, –13.6 to –12.9) and –10.3 mm Hg (95% CI, –10.5 to –10.1), respectively. Renin inhibitor: –13.5 mm Hg (95% CI, –14.2 to –12.9) and –11.3 mm Hg (95% CI, –11.7 to –10.9), respectively.

*Agent not available in the United States (US)
Drug regimen abbreviations: QAM=every morning, QD=once daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single blinded, SC=single centre, SR=sustained release, XO=crossover
Other abbreviations: β-blockers=β-adrenergic blocking agents, CCBs=calcium-channel blocking agents, DBP=diastolic blood pressure, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure

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 10. Relative Cost of the Thiazide-Like Diuretics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Chlorthalidone	tablet*	Thalitone®	$$	$
Indapamide	tablet	N/A	N/A	$
Metolazone	tablet	Zaroxolyn®*	$$$	$-$$

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

X. Conclusions

The thiazide-like diuretics are approved for the treatment of hypertension and edema associated with congestive heart failure.[1-8] Chlorthalidone and metolazone are also indicated for the treatment of edema due to renal dysfunction. Additionally, chlorthalidone is approved for the adjunctive treatment of edema associated with hepatic cirrhosis, as well as corticosteroid and estrogen therapy. All of the agents are available in a generic formulation.

Guidelines recommend the use of diuretics and sodium restriction for the management of ascites due to cirrhosis.[40-41] Spironolactone is recommended as first-line therapy, either as monotherapy or in combination with furosemide. Amiloride is an alternative treatment option in patients experiencing gynecomastia with spironolactone. Triamterene, metolazone and hydrochlorothiazide have also been used to treat ascites.

For the treatment of chronic heart failure, guidelines recommend the use of diuretics in all patients who have evidence of volume overload.[12,14-15] Loop diuretics are generally recommended as initial therapy in patients with left ventricular dysfunction.[14-15] For those with persistent fluid retention despite treatment with a loop diuretic, a thiazide diuretic or metolazone may be added to the regimen. In patients with normal left ventricular function, either a thiazide diuretic or loop diuretic may be used as initial therapy to manage fluid overload.[12,14]

There are several national and international organizations that have published guidelines on the treatment of hypertension.[13,16-19,21-23] Thiazide-type diuretics are frequently recommended as initial therapy in patients with uncomplicated hypertension, either as monotherapy or in combination with other agents.[13,16,19,23] According to the European Society of Hypertension guidelines, thiazide-type diuretics, ACE inhibitors, calcium-channel blocking agents, angiotensin II receptor antagonists and β-blockers do not differ in their ability to reduce blood pressure.[17-18] There is also no evidence that they differ in their ability to protect against cardiovascular risk or cause-specific cardiovascular events.[17-18]All of the available guidelines consistently recommend that the selection of an antihypertensive agent be based on compelling indications for use.[13,16-19,21-23] Most patients will need more than one antihypertensive medication to achieve blood pressure goals. In clinical trials, the thiazide-like diuretics have been shown to effectively lower blood pressure.[24-38] There were no studies found in the medical literature that directly compared the efficacy and safety of the thiazide-like diuretics for the treatment of hypertension.

There is insufficient evidence to support that one brand thiazide-like diuretic 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 thiazide-like diuretics 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 thiazide-like diuretic 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 Vasopressin Antagonists
AHFS Class 402828
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I. Overview

In July 2010, conivaptan and tolvaptan were moved from the miscellaneous diuretics class (AHFS 402892) to a new diuretic subclass, the vasopressin antagonists (AHFS 402828). Conivaptan is an injectable product which is FDA-approved to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.[2-4] Tolvaptan is an oral product that is approved for the treatment of clinically significant euvolemic and hypervolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).[1] The major disorders associated with euvolemic hyponatremia include SIADH, nephrogenic syndrome of inappropriate antidiuresis (NSIAD), glucocorticoid deficiency, hypothyroidism, exercise-associated hyponatremia (EAH), low solute intake and primary polydipsia.[5] Hypervolemic hyponatremia is most often caused by heart failure, cirrhosis, nephrotic syndrome, as well as acute and chronic renal failure.[5]

Hyponatremia is frequently associated with elevated plasma levels of arginine vasopressin (AVP). AVP is normally secreted in response to increased plasma osmolality, decreased blood volume, or decreased blood pressure.[5] Suppression of AVP secretion occurs when osmolality falls below a certain threshold, which results in renal excretion of free water. Failure to suppress AVP secretion may result in water retention and hyponatremia.[5] The use of traditional diuretics leads to both water and electrolyte excretion (diuresis); whereas, the use of tolvaptan leads to an increase in water excretion only (aquaresis), a decrease in urine osmolality, and an increase in serum sodium concentration.[1] Urinary excretion of sodium and potassium, as well as plasma potassium concentrations, are not significantly affected by tolvaptan.[1]

The management of hyponatremia depends on the clinical presentation and duration of the disease (acute versus chronic hyponatremia). Therapeutic options include treating the underlying disease (if possible), fluid restriction, sodium chloride administration and diuresis.[6] Patients with chronic mild hyponatremia are often asymptomatic and treatment consists of fluid restriction or isotonic saline administration.[6] Acute severe hyponatremia requires more aggressive initial therapy as it may increase morbidity and mortality.[5-6] Treatment of hyponatremia must be approached carefully as overly rapid correction may cause osmotic demyelination. Symptoms of osmotic demyelination are often irreversible and include quadriparesis, paraparesis, dysphagia, dysarthria, diplopia, seizures, coma and death.[5-6]

The vasopressin antagonists that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products currently available. This is a new class review; however, tolvaptan was previously reviewed as a new drug in February 2010.

Table 1. Vasopressin Antagonists Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Conivaptan	injection^	Vaprisol®	none
Tolvaptan	tablet	Samsca®	none

^Product is primarily administered in an institution.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the vasopressin antagonists are summarized in Table 2.

Table 2. Treatment Guidelines Using the Vasopressin Antagonists

Clinical Guideline	Recommendation(s)
American Journal of Medicine: **Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations[5] (2007)**	General Information • There are no data to suggest that the etiology of the hyponatremia, nor the methodology used to correct hyponatremia, alters the susceptibility for producing osmotic demyelination with overly rapid correction. • The rate of correction of hyponatremia must be taken into account before deciding on the most appropriate therapy for any patient with hyponatremia. • Patients with acute (<48 hours) hyponatremia may present with alarming neurologic findings, and they sometimes die of brain herniation. When hyponatremia develops over several days, brain swelling is minimized so that patients with chronic (<48 hours) hyponatremia have more modest symptoms and almost never die of brain herniation. Rate of Correction of Hyponatremia • In patients with chronic hyponatremia, neurologic sequelae are associated with more rapid rates of correction. The osmotic demyelination syndrome can usually be avoided by limiting correction of chronic hyponatremia to <10 to 12 mmol/L in 24 hours and to <18 mmol/L in 48 hours. These estimates should be regarded as approximate limits and not goals of therapy. • Patients with severe symptoms from chronic hyponatremia, particularly those with seizures, may benefit from a brief infusion of hypertonic saline, increasing the serum sodium by 2 to 4 mmol/L within 2 to 4 hours. There is no evidence that a quick but limited increase in the serum sodium is harmful; such therapy should not be considered "rapid" if the total increase in serum sodium over 24 hours is maintained at <10 mmol/L in 24 hours or <18 mmol/L in 48 hours. Conventional Therapy of Euvolemic Hyponatremia • Treatment of patients with euvolemic hyponatremia will vary greatly depending on their presentation. The single most important factor guiding initial therapy is the presence of neurologic symptoms. • Cases of acute hyponatremia (<48 hours in duration) are usually symptomatic if the hyponatremia is severe (<120 mmol/L). These patients are at greatest risk from neurologic complications from the hyponatremia itself and should be corrected to higher serum sodium levels promptly. • Patients with more chronic hyponatremia (>48 hours in duration) who have minimal neurologic symptomatology are at little risk from complications of hyponatremia itself, but can develop osmotic demyelination following rapid correction. There is no indication to correct these patients rapidly, and they should be treated using slower-acting therapies. • Syndrome of inappropriate antidiuretic hormone secretion (SIADH): o Correction of acute symptomatic hyponatremia is best accomplished with hypertonic (3%) saline given via continuous infusion. Intravenous furosemide 20 to 40 mg should be used to treat volume overload. Acute treatment should be discontinued when the patient's symptoms are abolished, a safe serum sodium level (≥120 mmol/L) is achieved, or a total correction of 18 mmol/L is achieved.

Clinical Guideline	Recommendation(s)
	○ For the treatment of mild-to-moderate chronic hyponatremia, fluid restriction represents the least toxic therapy, and has generally been the treatment of choice. Several days of restriction are usually necessary before a significant increase in plasma osmolality occurs. ○ Pharmacologic interventions are reserved for refractory cases where the degree of fluid restriction required to avoid hypo-osmolality is so severe that the patient is unable, or unwilling, to maintain it. The preferred drug is demeclocycline, which causes a nephrogenic form of diabetes insipidus. Treatment must be continued for several days to achieve maximal diuretic effects. Other agents, such as lithium, have similar renal effects but are less desirable because of inconsistent results and significant side effects and toxicities. Urea is as an alternative treatment for SIADH. • Glucocorticoid deficiency: ○ Glucocorticoid replacement should be started immediately after completion of a rapid ACTH stimulation test. Several days of glucocorticoids are sometimes required for normalization of the plasma osmolality. Primary treatment of hyponatremia may be indicated if significant neurologic symptoms are present. • Hypothyroidism: ○ The primary therapy of hypothyroidism is thyroid hormone replacement. ○ Hyponatremia with hypothyroidism is infrequent and generally of mild severity; therefore, modest fluid restriction is generally the only treatment necessary. ○ Symptomatic hyponatremia may be seen in patients with more severe hypothyroidism and altered mental status, primary treatment of hyponatremia may be indicated to ascertain whether the hyponatremia is contributing to the patient's neurologic symptoms. • Exercise-associated hyponatremia (EAH): ○ EAH can be severe and life threatening as a result of cerebral edema and noncardiogenic pulmonary edema. ○ Hyponatremia occurring in the setting of endurance exercise is acute, and treatment of symptomatic hyponatremia should be rapid. ○ With significant CNS impairment, hypertonic saline should begin immediately and continued until the serum sodium reaches 125 mmol/L or symptoms resolve. • Low solute intake: ○ Hyponatremia from low solute intake is corrected by instituting proper nutrition, with increased content of solute both as electrolytes and protein. • Primary polydipsia: ○ Therapy should be directed at reducing fluid intake into the normal range. ○ Fluid ingestion in patients with psychogenic causes of polydipsia responds variably to behavior modification and pharmacologic therapy (e.g., clozapine). <u>Conventional Therapy of Hypervolemic Hyponatremia</u> • For all diseases associated with edema formation, dietary sodium restriction and diuretic therapy are the mainstays of therapy. • Congestive heart failure (CHF):

Clinical Guideline	Recommendation(s)
	○ Currently, there are no guidelines specifically regarding treatment of hyponatremia in CHF. ○ Severely symptomatic hyponatremia is uncommon in CHF, but it can be treated with hypertonic saline provided adequate diuresis is established. However, the volume expansion associated with the use of hypertonic saline makes this an unattractive option for all but emergent situations. ○ Treatment of mild-to-moderate hyponatremia in CHF is largely empiric. Options include demeclocycline, urea, and fluid restriction. Difficulty in use and toxicity make demeclocycline and urea less attractive treatment options. Fluid restriction is not very effective or well tolerated. There are no outcomes studies available to guide the use of fluid restriction in acute or chronic CHF. • Cirrhosis: ○ There are no guidelines specifically regarding treatment of hyponatremia in cirrhosis. ○ Demeclocycline is relatively contraindicated because of a high incidence of nephrotoxicity, and urea has not been used often. Fluid restriction is the usual approach, but without outcome studies to assess its effectiveness. • Nephrotic syndrome, acute and chronic renal failure: ○ In patients with hyponatremia with advanced acute and chronic renal failure and GFR <20 mL/min, fluid restriction to amounts less than insensible losses plus urine output is generally necessary to cause a negative solute-free water balance and correction of hyponatremia. <u>Use of Vasopressin Receptor Antagonists in Hyponatremia</u> • For the treatment of acute severe hyponatremia, there is insufficient data from clinical trials to know if sufficiently rapid correction can be achieved with vasopressin receptor antagonists without the use of hypertonic saline. • Most studies to date in patients with hyponatremia have only been of relatively short duration. The most appropriate way to use these agents, their long-term response rates, how important the role of water restriction will remain during chronic use, and whether correction of chronic hyponatremia will result in improved cognitive function as suggested by 30-day studies of tolvaptan, and quality of life, or functional status, as suggested by initial studies of gait stability and falls, are unknown at the present time and will require additional study. • Safety issues must be considered carefully with any new class of drugs. The possibility of overcorrection has been of significant concern in all of the vasopressin receptor antagonist clinical trials, but to date osmotic demyelination has not been reported with any agent. The potential for serious drug interactions via interference with CYP3A4-mediated metabolism of other drugs must also be recognized. Whether there will be any adverse effect of V_2 receptor inhibition in vascular endothelium is unknown. • Further studies will be needed to assess the appropriate use of vasopressin receptor antagonists, such as for correction of symptomatic hyponatremia either alone or in conjunction with hypertonic saline infusions; to assess the benefits of correction of hyponatremia in hospitalized patients in terms of disease outcomes and decreased lengths of intensive care unit and hospital stay; and for long-term treatment of minimally symptomatic hyponatremia in order to decrease the risks of neurocognitive dysfunction and gait instability.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the vasopressin antagonists 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 Vasopressin Antagonists[1-4]

Indication	Tolvaptan*†
Treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)	✔

*Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with tolvaptan.
†It has not been established that tolvaptan provides a symptomatic benefit to patients.

IV. Pharmacokinetics

The pharmacokinetic parameters of the vasopressin antagonists are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Vasopressin Antagonists[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Tolvaptan	≥40	99	Liver, extensive	Non-renal routes	12

V. Drug Interactions

Significant drug interactions with the vasopressin antagonists are listed in Table 5. Tolvaptan is metabolized by CYP3A, and use with strong CYP3A inhibitors causes a marked (5-fold) increase in exposure.[1] Tolvaptan is contraindicated in combination with strong cytochrome CYP3A inhibitors, such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone and telithromycin.[1] The use of tolvaptan in combination with CYP3A inducers and moderate CYP3A inhibitors should also be avoided.[1]

Table 5. Significant Drug Interactions with the Vasopressin Antagonists[2]

Generic Name	Significance Level	Interaction	Mechanism
Tolvaptan	1	HIV protease inhibitors	Inhibition of CYP3A4 by HIV protease inhibitors may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by HIV protease inhibitors.
Tolvaptan	1	Imidazoles	Inhibition of CYP3A4 by imidazoles may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by imidazoles.
Tolvaptan	1	Macrolides and ketolides	Inhibition of CYP3A4 and P-glycoprotein by macrolides and ketolides may decrease the metabolic

Generic Name	Significance Level	Interaction	Mechanism
			elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by macrolides and ketolides.
Tolvaptan	1	Nefazodone	Inhibition of CYP3A4 by nefazodone may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by nefazodone.
Tolvaptan	2	Barbiturates	Induction of CYP3A isoenzymes by barbiturates may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by barbiturates compromising therapeutic effectiveness.
Tolvaptan	2	Carbamazepine	Induction of CYP3A isoenzymes by carbamazepine may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by carbamazepine compromising therapeutic effectiveness.
Tolvaptan	2	Hydantoins	Induction of CYP3A isoenzymes by hydantoins may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by hydantoins compromising therapeutic effectiveness.
Tolvaptan	2	Moderate CYP3A4 Inhibitors	Inhibition of CYP3A isoenzymes by moderate CYP3A4 inhibitors may decrease the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be increased by moderate CYP3A4 inhibitors.
Tolvaptan	2	Rifamycins	Induction of CYP3A isoenzymes by rifamycins may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by rifamycins compromising therapeutic effectiveness.
Tolvaptan	2	St. John’s wort	Induction of CYP3A isoenzymes by St. John's wort may increase the metabolic elimination of tolvaptan. Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by St. John's wort compromising therapeutic effectiveness.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the vasopressin antagonists are listed in Table 6. The boxed warning for tolvaptan is listed in Table 7.

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

Adverse Events	Tolvaptan
Cardiovascular	
Intracardiac thrombus	<2
Ventricular fibrillation	<2
Central Nervous System	
Cerebrovascular accident	<2
Pyrexia	4
Endocrine and Metabolic	
Diabetic ketoacidosis	<2
Hyperglycemia	6
Gastrointestinal	
Anorexia	4
Constipation	7
Ischemic colitis	<2
Nausea	21
Xerostomia	7-13
Genitourinary	
Pollakiuria	4-11
Polyuria	4-11
Urethral hemorrhage	<2
Vaginal hemorrhage	<2
Laboratory Abnormalities	
Prothrombin time prolonged	<2
Musculoskeletal	
Rhabdomyolysis	<2
Weakness	9
Respiratory	
Pulmonary embolism	<2
Respiratory failure	<2
Other	
Deep vein thrombosis	<2
Disseminated intravascular coagulation	<2
Thirst	12-16

✓ Percent not specified
- Event not reported

Table 7. Boxed Warning for Tolvaptan[1-2]

WARNING
Initiation of therapy: Initiate and reinitiate tolvaptan in patients only in a hospital where serum sodium can be closely monitored. **Monitor serum sodium:** Too rapid correction of hyponatremia (e.g., more than 12 mEq/L per 24 hours) can cause osmotic demyelination, resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, and death. In susceptible patients, including those with severe malnutrition, alcoholism, or advanced liver disease, slower rates of correction may be advisable.

VII. Dosing and Administration

The usual dosing regimens for the vasopressin antagonists are listed in Table 8.

Table 8. Usual Dosing Regimens for the Vasopressin Antagonists[1-4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Tolvaptan	Hypervolemic and Euvolemic Hyponatremia: Initial: 15 mg once daily; increase to 30 mg once daily after ≥24 hours, to a maximum of 60 mg once daily, as needed to achieve the desired level of serum sodium.	Safety and effectiveness have not been established in pediatric patients.	Tablet: 15 mg 30 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the vasopressin antagonists are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Vasopressin Antagonists

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gheorghiade et al.[11] (2006) Tolvaptan 10 mg daily, with titration to larger doses (15, 30, 45, and 60 mg/day) as needed to achieve serum sodium concentrations within normal limits vs fluid restriction (initially 1,200 ml/24 hours) plus placebo	RCT, MC, OL, AC Inpatients ≥18 years, serum sodium <135 mmol/L for ≥2 consecutive days, and normovolemia or signs of fluid overload	N=28 Inpatient treatment: 14 days Outpatient treatment: 14 days Follow-up: 65 days	Primary: Normalization of serum sodium concentration (defined as ≥135 mmol/L or an increase of >10% from baseline to the last inpatient assessment) Secondary: Changes in serum sodium from baseline to the last outpatient visit (day 65), urine osmolality, urine volume, urine sodium concentration, body weight, total fluid intake, and thirst score from baseline to the last inpatient assessment	Primary: A higher proportion of subjects in the tolvaptan group had achieved the normalization of serum sodium compared with those in the fluid restriction group by the last inpatient visit (P=0.049). The normalization of serum sodium was achieved more rapidly in the tolvaptan group than in the fluid restriction group, occurring in 50% of tolvaptan-treated subjects by day 4, compared with day 8 in the fluid restriction group (P<0.03). Patients in the tolvaptan group had a significantly greater increase in serum sodium concentration 4 hours after the first dose (1.6 mmol/L; P=0.016), at day 5 (5.2 mmol/L; P=0.019) and at the last inpatient visit (5.7 mmol/L; P=0.0065) compared to patients receiving fluid restriction (-0.8 mmol/L, 0.7 mmol/L and 1 mmol/L, respectively). Secondary: At day 65, the mean change in serum sodium was 4.7 mmol/L in the tolvaptan group compared to -0.3 mmol/L in the placebo group (P=0.039). Urine sodium was significantly lower (P=0.021) and urine output was significantly greater (P=0.014) in the tolvaptan group compared to the placebo group. No significant differences in urine osmolality (P=0.058), serum potassium (P=0.45), blood pressure, heart rate, body weight (P=NS), thirst score (P=0.8) or adverse events requiring drug discontinuation were observed between the treatment groups.
Schrier et al.[12] (2006) SALT-1 and SALT-2	RCT, MC, DB, PC Patients ≥18 years of age with euvolemic or	N=102 (SALT-1) N=123 (SALT-2)	Primary: Change in the average daily AUC for the serum sodium from	Primary: By day 4, the increase in the average daily AUC for the serum sodium concentration was 3.62 and 4.33 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 0.25 and 0.42 for placebo (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tolvaptan 15 mg daily for 30 days (dose could be titrated to 60 mg daily) vs placebo	hypervolemic hyponatremia (serum sodium <135 mmol/L). Patients also had chronic heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with the hyponatremia.	37 days	baseline to day 4 and from baseline to day 30 Secondary: Change in the AUC for the serum sodium in patients with marked hyponatremia, serum sodium concentration at each visit, time to normalization of the serum sodium, percent of patients with serum sodium concentrations that normalized at day 4 and day 30, serum sodium concentration on day 4 and day 30 for patients with mild or marked hyponatremia at baseline, change from baseline in scores on the Physical Component Summary and Mental Component Summary of the Medical Outcomes Study 12-item Short-Form (SF-	By day 30, the increase in the average daily AUC for the serum sodium concentration was 6.22 and 6.20 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 1.66 and 1.84 for placebo (P<0.001 for all comparisons). Secondary: By day 30, the increase in the average daily AUC for the serum sodium concentration in patients with marked hyponatremia was 8.24 and 7.60 for tolvaptan (SALT-1 and SALT-2, respectively) compared to 2.54 and 2.72 for placebo (P<0.001 for all comparisons). By day 4, serum sodium concentrations were 133.9 mmol/L and 135.3 mmol/L for tolvaptan (SALT-1 and SALT-2, respectively) compared to 129.7 mmol/L and 129.6 mmol/L for placebo (P<0.001 for all comparisons). By day 30, serum sodium concentrations were 135.7 mmol/L and 135.9 mmol/L for tolvaptan (SALT-1 and SALT-2, respectively) compared to 131 mmol/L and 131.5 mmol/L for placebo (P<0.001 for all comparisons). By day 4, 40% and 55% of patients receiving tolvaptan (SALT-1 and SALT-2, respectively) had normal serum sodium concentrations compared to 13% and 11% for placebo (P<0.001 for all comparisons). By day 30, 53% and 58% of patients receiving tolvaptan (SALT-1 and SALT-2, respectively) had normal serum sodium concentrations compared to 25% and 25% for placebo (P<0.001 for all comparisons). Scores on the Physical Component Summary did not differ significantly between groups. Scores for the Mental Component Summary improved in the tolvaptan group when the data from SALT-1 and SALT-2 were combined (P=0.02), as well as in SALT-1 (P=0.04). Scores improved significantly in the combined subgroup of patients with marked hyponatremia (P=0.04). There was no significant difference between the groups found in SALT-2 (P=0.14). Adverse event profiles in the two study groups were similar for all comparisons. The most common adverse events occurring during the study

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			12) General Health Survey	in the tolvaptan groups were thirst and dry mouth. Overall, there were 26 serious adverse events potentially related to the study treatment in SALT-1 and SALT-2. The number of deaths in the two study groups was similar (14 deaths among 223 patients in the tolvaptan groups and 13 deaths among 220 patients in the placebo groups), and they occurred within the defined observation period. In 4 of the patients in the tolvaptan group, the desirable rates of sodium correction were exceeded during the first 24 hours of the study (>0.5 mmol/L per hour). In 4 patients (1.8%), the predefined serum sodium concentration (>146 mmol per liter) was exceeded.
Berl et al.[15] (2010) SALTWATER Tolvaptan once daily (dose varied based on response)	OL, ES (Extension of SALT-1 and SALT-2) Patients ≥18 years of age with euvolemic or hypervolemic hyponatremia (serum sodium <135 mmol/L). Patients also had chronic heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with the hyponatremia.	N=111 4 years (mean 1.9 years)	Primary: Safety and efficacy	Primary: During the follow-up period, 105 of 111 patients experienced an adverse event (AE). The most common AEs that were potentially related to tolvaptan use were pollakiuria, thirst, fatigue, dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral edema, and acute renal failure. A total of 19 patients died during the follow-up period (9 deaths per 100 patient-years of exposure). The death rate during SALTWATER was lower than that observed for SALT (86.9 deaths per 100 patient-years of exposure). In 5 patients, serum sodium correction exceeded the rate of 1 mmol/L per h at the 8-hour time point. There were 18 patients who had serum sodium levels >145 mmol/L at individual time points. Correction of serum sodium levels during the first 8 hours of therapy occurred at similar rates in SALTWATER compared to SALT-1 and SALT-2. After the initial titration period, mean serum sodium levels remained within the normal range throughout the 4-year treatment period. In all patient subgroups, serum sodium levels declined by 7 days of withholding tolvaptan. On drug discontinuation, the proportion of patients who declined by at least 3 mEq/L was 68%, and an equal proportion fell from ≥135mEq/L to below this threshold of normal.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The mean time to first fluid restriction was 122.3 and 162.5 days in the mild and marked hyponatremia subgroups, respectively; 13.2% of patients in the mild hyponatremia group and 5.4% in the marked hyponatremia group required fluid restriction.
Udelson et al.[7] (2008) Tolvaptan 15mg, 30 mg, or 60 mg administered as a single dose vs placebo	RCT, MC, DB, PC Patients ≥18 years of age with symptomatic heart failure (New York Heart Association functional class III or IV) of at least 3 months' duration caused by left ventricular ejection fraction <40%. Patients were also required to be on standard background therapy for heart failure for at least 1 month.	N=181 12 hours	Primary: Pulmonary capillary wedge pressure (PCWP) peak change from baseline within 3 to 8 h after treatment administration Secondary: Area under the curve (AUC) for the change from baseline PCWP and other hemodynamic parameters over an 8 hour evaluation period and renal and electrolyte parameters	Primary: The pairwise comparisons of 15, 30, and 60 mg tolvaptan versus placebo each showed a statistically significant decrease in peak change in PCWP from 3 to 8 hours post-dose (P=0.003, P=0.044, and P=0.033, respectively). Secondary: For the AUC0-8h, the 15-mg tolvaptan group was the only tolvaptan dose group that was statistically significantly different from placebo. All tolvaptan doses produced statistically significantly greater changes than placebo in peak change in pulmonary artery pressure (P<0.01 for 15 mg; P<0.05 for 30 mg and 60 mg). Tolvaptan 15- and 30-mg doses resulted in statistically significant reductions in peak change in right atrial pressure as compared with placebo (P<0.01 and P<0.05, respectively). No significant changes in cardiac index, pulmonary vascular resistance, and systemic vascular resistance were observed after tolvaptan administration compared with placebo. The single dose of tolvaptan produced a dose-dependent increase in urine output (P<0.0001 for all tolvaptan groups vs placebo). Urine osmolality was significantly reduced by all doses of tolvaptan relative to placebo (P<0.0001 for all tolvaptan groups vs placebo). Free water clearance was significantly greater for all tolvaptan doses relative to placebo at all time points. Plasma osmolality increased in all of the tolvaptan-treated groups compared with placebo. Serum sodium levels showed a dose-related increase compared with placebo (1.2 mEq/L, 3.3 mEq/L, 4.6 mEq/L, and -0.7 mEq/L for the tolvaptan 15-mg, 30-mg, 60-mg, and placebo groups, respectively). Potassium levels were not different from placebo in any of the tolvaptan dosing groups. No significant changes in serum creatinine,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				blood urea nitrogen, serum potassium, and vital signs were observed after study drug administration. Tolvaptan was well tolerated relative to placebo. Patient-reported adverse events in this short-term study occurred in 45.5%, 44.2%, 54.3%, and 33.3% of the 15-, 30-, and 60-mg tolvaptan and placebo groups, respectively.
Udelson et al.[8] (2007) Tolvaptan 30 mg daily vs placebo	RCT, MC, DB, PC Patients ≥18 years of age with congestive heart failure (New York Heart Association functional class II to III) with a left ventricular ejection fraction <30%. Patients were also required to be on standard background therapy for heart failure for at least for 3 months before enrollment.	N=240 55 weeks	Primary: Change from baseline in left ventricular end diastolic volume (LVEDV) index Secondary: Change from baseline in left ventricular end systolic volume (LVESV) index, comparison of the change from baseline in LVEDV index after drug withdrawal (week 55), and assessment of symptoms (using subject-assessed symptom scales and the Minnesota Living With Heart Failure Questionnaire)	Primary: In the placebo group, there was no change in LVEDV index over the year of follow-up. After 1 year of tolvaptan therapy, there was a small reduction in LVEDV index; however, this was not significantly different from placebo (-1.8 ml/m^2; P=0.21 vs placebo). There was also no difference in the change of volumes from baseline at the week 55 study. Secondary: In the placebo group, LVEDV index decreased 0.4 ml/m^2 compared to a decrease of 3.3 ml/m^2 in the tolvaptan group (P=0.09). There was no difference in the change of LVESV index from baseline at week 55. Ejection fraction changes were small and similar in both treatment groups. Only minor changes in blood pressure and heart rate were observed over the course of the trial; there were no significant differences in the tolvaptan versus placebo groups. There were no significant between-group differences in serum sodium or potassium across the course of the trial. There were also no differences in renal function parameters (BUN and serum creatinine) across the year of therapy. No statistically significant differences were observed between the tolvaptan group and the placebo group for the change from baseline in Minnesota Living With Heart Failure Questionnaire score or for the Visual Analog Scale assessment of global status or respiratory status. More subjects in the tolvaptan group reported a score of “better” in the subject-assessed overall treatment effect at each visit than did subjects in the placebo group; however, no statistically significant differences were observed between treatment groups. There were 6 deaths (5%) and 21 hospitalizations of patients with heart

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				failure (18%) in the tolvaptan-treated group, compared with 11 deaths (9%) and 34 heart failure hospitalizations (28%) in the placebo-treated group (P<0.03 for the composite of death and heart failure hospitalizations). Adverse events including urinary frequency, thirst, and dry mouth occurred more frequently with tolvaptan than with placebo therapy. There was no difference in the number of patients withdrawn from the trial as the result of bothersome side effects between the 2 randomization groups.
Gheorghiade et al.[9] (2007) EVEREST Tolvaptan 30 mg daily within 48 hours of admission vs placebo	RCT, MC, DB, PC Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening congestive heart failure and who had a left ventricular ejection fraction ≤40%. Patients also received conventional heart failure therapy.	N=2,048 (trial A) N=2,085 (trial B) 7 days	Primary: Composite score of changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge Secondary: Patient-assessed changes in dyspnea at day 1, global clinical status at day 7 or discharge, body weight at days 1 and 7 or discharge, and peripheral edema at day 7 or discharge	Primary: The composite score of changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge was greater with tolvaptan compared to placebo (trial A, mean 16 vs 0.99; P<0.001; trial B, mean 17 vs 0.97; P<0.001). Improvement in patient-assessed global clinical status (assessed alone), measured by a 100-point visual analog scale at day 7 or discharge, was similar between the tolvaptan and placebo groups (trial A, mean 18.25 vs 17.73; P=0.51; trial B, mean 18.72 vs 18.28; P=0.52). Mean body weight reductions at day 7 or discharge in the tolvaptan and placebo groups were 3.35 kg vs 2.73 kg, respectively, in trial A (P<0.001) and 3.77 kg vs 2.79 kg, respectively, in trial B (P<0.001). Secondary: More patients in the tolvaptan groups (76.74% in trial A and 72.06% in trial B) reported an improvement dyspnea at day 1 (for those patients with dyspnea at baseline) compared to placebo (70.61% in trial A and 65.32% in trial B; P<0.001 in both trials). There was no significant difference in global clinical status at day 7 or discharge between the tolvaptan or placebo treatment groups (trial A, P=0.51; trial B, P=0.52). Changes in mean body weight were significantly greater with tolvaptan at day 1 (trial A, -1.71 kg; trial B -1.82 kg) than with placebo (trial A, -0.99 kg; trial B, 0.95 kg; P<0.001 in both trials).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in peripheral edema at inpatient day 7 or discharge with tolvaptan vs placebo in trial A. In trial B, 73.67% of patients experienced at least a 2-grade improvement in pedal edema with tolvaptan compared to placebo (P=0.02). An overall in-hospital mortality rate of 2.4% and 2.9% was observed in the tolvaptan and placebo groups, respectively. Through day 7 or discharge, adverse events were reported in 49.1% and 40.0% of patients in trial A, and in 55.9% and 47.9% of patients in trial B in the tolvaptan and placebo groups, respectively.
Konstam et al.[10] (2007) EVEREST Tolvaptan 30 mg daily within 48 hours of admission vs placebo	RCT, MC, DB, PC Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening congestive heart failure and who had a left ventricular ejection fraction ≤40%. Patients also received conventional heart failure therapy.	N=4,133 ≥60 days	Primary: All-cause mortality and the composite of cardiovascular death or hospitalization for HF Secondary: Composite of cardiovascular mortality or cardiovascular hospitalization, incidence of cardiovascular mortality, incidence of clinical worsening of HF (death, hospitalization for HF, or unscheduled visit for HF), changes from baseline in body weight at day	Primary: The median duration of follow-up was 9.9 months. A total of 537 patients in the tolvaptan group (25.9%) and 543 patients in the placebo group (26.3%) died (HR, 0.98; 95% CI, 0.87- 1.11; P=0.68). A total of 871 patients in the tolvaptan group (42.0%) and 829 patients in the placebo group (40.2%) died from cardiovascular causes or had a first hospitalization for HF (HR, 14; 95% CI, 0.95-1.14; P=0.55). Secondary: The composite of cardiovascular death or cardiovascular hospitalization, the incidence of cardiovascular mortality, and the incidence of clinical worsening of HF did not differ between the 2 treatment groups (P=0.52, P=0.67 and P=0.62, respectively). In patients with dyspnea at baseline, patient-assessed dyspnea scores significantly improved at day 1 in patients receiving tolvaptan compared with placebo (P<0.001), with 74.3% of the tolvaptan group and 68.0% of the placebo group demonstrating an improvement in dyspnea score. Mean body weight at day 1 was reduced by 1.76 kg in the tolvaptan group and by 0.97 kg in the placebo group (P<0.001). Among patients with baseline serum sodium levels less than 134 mEq/L, mean serum sodium concentrations increased by 5.49 mEq/L at day 7 or discharge with tolvaptan compared with 1.85 mEq/L in the placebo group (P<0.001). This effect was observed as early as day 1 and was maintained

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			1, serum sodium level at day 7 or discharge, edema score at day 7 or discharge, patient-assessed dyspnea at day 1, and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at outpatient week 1	through 40 weeks of treatment. In patients with baseline pedal edema, edema scores significantly improved at day 7 or discharge in patients receiving tolvaptan compared with placebo (P=0.003), with 73.8% of tolvaptan patients and 70.5% of placebo patients manifesting improvement in edema by at least 2 grades. A significant improvement in physician assessed pedal edema was observed as early as day 1 and continued through post discharge week 4. No significant changes were observed at outpatient week 1 in the KCCQ overall summary score. Statistically significant changes favoring tolvaptan were observed at the time of the last scheduled on-treatment assessment at study end for the quality-of life domain (P=0.003), the social limitation domain (P=0.05), and the overall summary score (P=0.02). The other domains (clinical summary, physical limitation, total symptom, symptom frequency, symptom burden, symptom stability, and self-efficacy) did not reach significance at the time of the last on-treatment assessment. Adverse events occurred in 89.0% of tolvaptan patients and 86.1% of placebo patients.
Pang et al.[16] (2009) EVEREST Tolvaptan 30 mg daily within 48 hours of admission vs placebo	RCT, MC, DB, PC (Post-hoc analysis) Patients ≥18 years of age with a history of chronic heart failure who had been hospitalized for worsening congestive heart failure with LVEF ≤40%. Patients also received conventional heart failure therapy.	N=3,664 1-3 days	Primary: Patient-assessed dyspnea using a seven-point Likert scale administered on day 1 after randomization	Primary: Tolvaptan was associated with improved patient-assessed dyspnea on inpatient Day 1 compared to placebo (74.3% vs 68.0%; P<0.0001) as reported in the primary EVEREST analysis. The greatest treatment differences were seen in subjects with continuous dyspnea at baseline. Patients were divided post hoc into five groups, based on time (in hours) of dyspnea assessment after the first dose of tolvaptan. The percentage improvement with placebo stayed relatively constant, whereas improvement with tolvaptan was greatest when measured early (P<0.05). The majority of patients had an improvement in dyspnea at all time points relative to hospital admission; however, there was a significantly higher rate of improvement with tolvaptan compared with placebo (P<0.05). There was also a linear association between reductions in body weight and improvements in patient-assessed dyspnea.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gheorghiade et al.[13] (2004) ACTIV IN CHF Tolvaptan 30 mg, 60 mg, or 90 mg daily vs placebo	RCT, MC, DB, PC Patients ≥18 years of age admitted for worsening congestive heart failure with left ventricular ejection fraction <40% within 1 year of admission and systemic congestion (jugular venous distention [JVD], rales, or peripheral edema after initial in-hospital therapy for heart failure). Patients also received conventional heart failure therapy.	N=319 Inpatient: 10 days Outpatient: 7 weeks	Primary: Change in body weight at 24 hours after the administration of the first dose of study drug; worsening heart failure at 60 days Secondary: Changes in dyspnea, JVD, rales, edema, body weight, urine output, serum electrolyte levels, length of hospital stay after randomization, use of diuretics, and patient/physician-assessed symptom scales	<u>Inpatient Phase</u> Primary: A greater median reduction in body weight was found in patients treated with tolvaptan compared to placebo 24 hours after the administration of the first dose of study drug (−1.80, −2.10, −2.05, and −0.60 kg for tolvaptan 30, 60, and 90 mg, and placebo, respectively; P=0.002, P=0.002, and P=0.009 for the 3 tolvaptan groups compared with the placebo group). Secondary: The median body weight reductions from baseline to discharge were greater in the tolvaptan groups compared with the placebo group (−3.30, −2.80, −3.20, and −1.90 kg in the groups receiving tolvaptan 30, 60, and 90 mg, and placebo, respectively; P=0.006, P=0.002, and P=0.06 for the 3 tolvaptan groups compared with placebo). The mean urine output at 24 hours was 4056.2, 4175.2, 4127.3, and 2296.5 mL for the tolvaptan 30, 60, and 90 mg, and placebo groups, respectively (P =0.02, P<0.001, and P<0.001 for the 3 tolvaptan groups compared with the placebo group). Signs and symptoms of heart failure improved in all patients during the period of hospitalization. There were no significant differences in JVD, and peripheral edema between the treatment groups (dyspnea P=0.04). Global assessment scales did not show a significant difference among the treatment groups. The median length of time between randomization and discharge was 4 days in both treatment groups. <u>Outpatient Phase</u> Primary: There was no significant difference in worsening heart failure between the tolvaptan groups and the placebo group. Secondary: Diuretic use decreased in all patients after discharge. There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant difference in mean dose reduction between the treatment groups.
Gheorghiade et al.[14] (2003) Tolvaptan 30 mg, 45 mg, or 60 mg daily vs placebo	RCT, DB, MC, PC Patients ≥18 years of age with a diagnosis of congestive heart failure irrespective of left ventricular ejection fraction. Patients also received conventional heart failure therapy.	N=254 25 days	Primary: Changes in body weight Secondary: Ankle edema measurements, urine sodium excretion, urine volume, urine osmolality, and safety	Primary: Mean decreases from baseline in body weight were observed on the first day of tolvaptan treatment at all doses and maintained throughout the study (P<0.001 vs placebo). The decrease in body weight was similar in all tolvaptan-treated patients irrespective of the LVEF. Patients receiving placebo experienced an increase in body weight from baseline. Secondary: Improvements in ankle edema scores were significantly better with tolvaptan 45 mg compared to placebo (P<0.05). None of the other doses studies differed significantly from placebo. Tolvaptan-treated patients had significantly greater mean total urinary sodium excretions (339.9, 373.0, and 355 mEq for the 30-, 45-, and 60-mg tolvaptan groups, respectively) than placebo-treated patients (193.7 mEq; P<0.05). Urine volumes were greater in tolvaptan-treated patients (3909, 4232, and 4597 mL for the 30-, 45-, and 60-mg tolvaptan groups, respectively) than in placebo-treated patients (2328 mL; P<0.05). At day 1, urine osmolality decreased by 15.5, 52.4, and 118.8 mOsm/kg in the 30-, 45-, and 60-mg tolvaptan groups, respectively compared to an increase of 135.8 mOsm/kg in the placebo group (P<0.05 for all comparisons). No significant differences were found between the tolvaptan groups and the placebo group in the quality-of-life assessment. No changes in heart rate or systolic or diastolic blood pressure, supine or standing, were observed in the tolvaptan groups during the study. Dry mouth, thirst, and polyuria, including urinary frequency, were higher in the tolvaptan-treated patients.

Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SC=single center

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 10. Relative Cost of the Vasopressin Antagonists

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Tolvaptan	tablet	Samsca®	$$$$$	N/A

N/A=Not available

X. Conclusions

Tolvaptan is approved for the treatment of clinically significant euvolemic and hypervolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction).[1] The management of hyponatremia depends on the clinical presentation and duration of the disease. Treatment must be approached carefully as overly rapid correction of hyponatremia (>12 mEq/L per 24 hours) may cause osmotic demyelination.

There are limited guidelines available that discuss the management of hyponatremia. An expert panel provided treatment recommendations in 2007, which includes fluid restriction, sodium chloride administration and diuresis.[5] The panel concluded that the optimal use of the vasopressin receptor antagonists has not been determined and further studies are needed.

Three short-term studies were conducted in a small number of patients with euvolemic or hypervolemic hyponatremia.[11-12] The results demonstrated significant improvements in serum sodium concentrations compared

to fluid restriction or placebo. An open-label, long-term extension study (mean follow-up of 701 days) assessed the drug-related adverse effects of tolvaptan and maintenance of efficacy.[15] The authors concluded that prolonged administration of tolvaptan maintained an increased serum sodium level with an acceptable margin of safety. Several other studies have evaluated the use of tolvaptan in patients with congestive heart failure as an add-on to conventional treatments.[7-10,13-14] Significant changes in body weight have been observed; however, the long-term use of tolvaptan (median duration 9.9 months) failed to demonstrate any improvements in mortality or hospitalizations for worsening heart failure.[10]

Data supporting the use of tolvaptan are limited. It has not been established that raising serum sodium with tolvaptan provides a symptomatic benefit to patients.[1] Patients requiring intervention to raise serum sodium urgently should not be treated with tolvaptan.[1] Hospitalization is required for initiation and reinitiation of tolvaptan therapy so that serum sodium can be monitored closely.[1]

There is insufficient evidence to conclude that tolvaptan offers a significant clinical advantage over other alternatives in general use. Since tolvaptan is not indicated as first-line therapy for the management of hyponatremia, it should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand vasopressin antagonists 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 vasopressin antagonist 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 Diuretics, Miscellaneous
AHFS Class 402892
November 10, 2010

I. Overview

In July 2010, conivaptan and tolvaptan were moved from the miscellaneous diuretics class (AHFS Class 402892) to the vasopressin antagonists class (AHFS Class 402828). Currently, there are no drugs classified by AHFS as miscellaneous diuretics.

II. Conclusions

There are no drugs available in the miscellaneous diuretics class (AHFS Class 402892).

III. Recommendations

No brand miscellaneous diuretic is recommended for preferred status. Alabama Medicaid should continue to include AHFS Class 402892 in the PDL screening process. If new outpatient miscellaneous diuretics are added, it is recommended that this class be re-reviewed at that time.

Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Acute Myocardial Infarction
November 10, 2010

I. Overview

Acute myocardial infarction (MI) is a clinical acute coronary syndrome resulting from obstruction of a coronary artery. Different degrees of obstruction result in different outcomes, which can include unstable angina, non–ST-segment-elevation MI (NSTEMI), and ST-segment elevation MI (STEMI). ST-segment elevation refers to elevations of the ST-segment on echocardiogram (ECG); Q waves may or may not be present.[1] ST-segment elevations and Q waves are absent in an NSTEMI.[1] Myocardial necrosis results from the reduction in oxygen supply to the infarcted tissue. Atherosclerosis of the coronary arteries is an essential part of this process in most cases. Infarction may occur when an atherosclerotic plaque erodes or ruptures, causing thrombosis formation, or when cardiac work exceeds the ability of the coronary artery to meet the metabolic needs of the myocardium.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of acute myocardial infarction are summarized in Table 1.

Table 1. Current Treatment Guidelines for Acute Myocardial Infarction

American College of Cardiology (ACC)/American Heart Association (AHA): 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update)[2] (2009)
Initial and Hospital Management • Oxygen, morphine, nitroglycerin (NTG), angiotensin-converting enzyme inhibitors (ACE inhibitors), β-adrenergic blocking agents (β-blockers), and aspirin may be used in patients presenting with an MI. Patients should be considered for reperfusion therapy. • Patients that did not receive β-blockers within 24 hours of ST-Elevation Myocardial Infarction (STEMI) should be started on these agents unless contraindicated. • Patients with early contraindications to β-blockers within 24 hours of STEMI should be reevaluated for candidacy for β-blocker therapy as secondary therapy. • All patients should continue receiving β-blockers unless contraindicated. • Patients undergoing facilitated percutaneous intervention (PCI), may be treated with high dose aspirin and/or fibrinolytic therapy. • It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists (abciximab, tirofiban or eptifibatide) at the time of primary PCI (with or without stenting) in selected patients with STEMI. • A loading dose of thienopyridine is recommended for STEMI patients for whom PCI is planned. • Clopidogrel should be initiated with aspirin and continued for 14 days regardless of whether reperfusion with fibrinolytic therapy is performed. Secondary Prevention • Smoking cessation is advised, in addition to avoidance of secondhand smoke. • For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with β-blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure.

- It may be reasonable to encourage the consumption of omega-3 fatty acids in the form of food or capsules.
- Low-density lipoprotein cholesterol (LDL-C) levels should be maintained at <100 mg/dL; <70 mg/dL is also reasonable. If LDL-C levels are ≥100 mg/dL, LDL-C lowering therapy should be initiated.
- Niacin, fibric acid derivatives (fibrates), or more intensive LDL-C lowering therapy may be beneficial in lowering non–high-density lipoprotein cholesterol (non–HDL-C) levels.
- Physical activity and weight management should be encouraged.
- It is recommended to initiate lifestyle and pharmacotherapy to achieve near-normal A1C levels.
- Aspirin therapy is recommended (unless contraindicated) at a dose of 162-325 mg for all patients post-PCI 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 75-362 mg.
- Clopidogrel should be given for at least 14 days to patients not undergoing stent placement.
- In patients receiving a stent (BMS or drug-eluting stent [DES]) during PCI for ACS, clopidogrel 75 mg daily or prasugrel 10 mg daily should be given for at least 12 months. If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered.
- Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing drug-eluting stent placement.
- Initiating and managing warfarin to an international normalized ratio (INR) of 2.0-3.0 is recommended in post-MI 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.
- ACE inhibitors should be started and continued indefinitely in all patients recovering from STEMI with LVEF ≤40% and for those with hypertension, diabetes, or chronic kidney disease, unless contraindicated.
- ACE inhibitors should be started and continued indefinitely in patients recovering from STEMI who are not lower risk (lower risk defined as those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed), unless contraindicated.
- Among lower risk patients recovering from STEMI (i.e., those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed) use of ACE inhibitors is reasonable.
- Use of angiotensin receptor blockers is recommended in patients who are intolerant of ACE inhibitors and have HF or have had an MI with LVEF ≤40%.
- It is beneficial to use angiotensin receptor blocker therapy in other patients who are ACE-inhibitor intolerant and have hypertension.
- Considering use of angiotensin receptor blockers in combination with ACE inhibitors in systolic dysfunction HF may be reasonable.
- Use of aldosterone blockade in post-MI patients without significant renal dysfunction or hyperkalemia is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and β-blocker, have an LVEF of ≤40%, and have either diabetes or HF.
- It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or LV dysfunction with or without HF symptoms, unless contraindicated.
- Annual influenza vaccination is recommended for all patients with cardiovascular disease (CVD).

European Society of Cardiology (ESC): Management of Acute Myocardial Infarction in Patients Presenting With ST-segment Elevation[4]
(2008)

Prophylactic Therapies in the Acute Phase

- In the absence of contraindications, all patients should receive aspirin, a thienopyridine (clopidogrel or prasugrel) and one of the following anticoagulants as soon as possible: bivalirudin or heparin, if primary PCI will be performed; enoxaparin or heparin, if a fibrin-specific lytic agent is given; fondaparinux, enoxaparin or heparin, if streptokinase is given.
- Anticoagulant therapy should be stopped shortly after the PCI procedure or after 24 to 48 hours in case of fibrinolytic therapy.
- An oral ACE inhibitor should be given on the first day in the absence of contraindications in patients with significant LV dysfunction.
- Routine intravenous administration of a β-blocker is not indicated. An oral β-blocker should be given as

soon as the patient is stable.

- Statins should be initiated as soon as possible to achieve an LDL cholesterol <100 mg/dl or <80 mg/dl if feasible irrespective of the initial cholesterol level. Risk factors for atherosclerosis should be identified and treatment started before hospital discharge.
- At discharge and in the absence of contraindications, all patients should be treated with ASA, a thienopyridine, a β-blocker and a statin. In patients with significant LV dysfunction, an ACE inhibitor (or an ARB) should be added. With the exception of the thienopyridine, these medications should be given indefinitely.
- Routine use of lidocaine is not justified due to an increased risk of asystole.
- Routine use of nitrates in the initial phase of MI has not shown to be of convincing value and is not recommended.
- There is no case for using calcium-channel blocking agents for prophylactic purposes in the acute phase of an MI.
- Recent trials have failed to demonstrate that the use of magnesium provides a benefit, and it is not recommended for routine use.

Secondary Prevention

- Smoking cessation is advised.
- Aspirin indefinitely (75–100 mg daily) in all patients without contraindications.
- Clopidogrel (75 mg daily) for 12 months in all patients irrespective of the acute treatment.
- Clopidogrel (75 mg daily) in all patients with contraindication to aspirin.
- Oral anticoagulant at INR 2–3 in patients who do not tolerate aspirin and clopidogrel.
- Oral β-blockers for all patients, regardless of blood pressure of LV function, unless contraindicated.
- ACE inhibitor in all patients without contraindications, regardless of blood pressure or LV function.
- Angiotensin receptor blockers in all patients without contraindications who do not tolerate ACE inhibitors, regardless of blood pressure or LV function.
- The use of verapamil and diltiazem may be appropriate when β-blockers are contraindicated, especially in obstructive airways disease.
- Dihydropyridines should only be prescribed for clear clinical indications, such as hypertension or angina.
- Nitrates should be used only in the presence of angina pectoris.
- Aldosterone blockade may be considered for post-STEMI patients with an EF <40% and heart failure or diabetes provided that creatinine is <2.5 mg/dL in men and <2.0 mg/dL in women, and potassium is ≤5.0 mEq/L.
- Statins in all patients, in the absence of contraindications, irrespective of cholesterol levels, initiated as soon as possible to achieve LDL cholesterol <100 mg/dL.
- Fibrates and omega-3 supplements should be considered in patients who do not tolerate statins, especially if triglycerides are >150mg/dL and/or HDL is <40mg/dL.
- Influenza immunization is indicated in all patients with coronary artery disease and thus also in those surviving a STEMI.

National Institute for Health and Clinical Excellence (NICE): Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction[3] (2007)

Secondary Prevention

- All patients who have had an acute MI should be offered treatment with a combination of the following drugs: ACE inhibitor, aspirin, β -blocker, and statin.
- ACE inhibitors are recommended early after presentation with an acute MI.
- After an MI, all patients with preserved left ventricular function or with left ventricular systolic dysfunction should continue treatment with an ACE inhibitor indefinitely, whether or not they have symptoms of heart failure.
- Routine use of angiotensin receptor blockers after an acute MI is not recommended.
- Angiotensin receptor blockers are recommended in patients who are intolerant to ACE inhibitor therapy.
- Combination therapy with an ACE inhibitor and an angiotensin receptor blocker is not routinely recommended in patients early after an acute MI with heart failure and/or left ventricular systolic

dysfunction.

- Aspirin is recommended in all patients after an MI and should be continued indefinitely.
- Clopidogrel should not be offered as first-line monotherapy after an MI.
- Clopidogrel combined with low-dose aspirin for 12 months is recommended in patients who have had a non–ST-segment-elevation ACS and who are at moderate-to-high risk of MI or death. Thereafter, patients may be treated with 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 STEMI should continue on dual antiplatelet therapy for at least 4 weeks. Thereafter, clopidogrel may be discontinued in the absence of indication for dual antiplatelet therapy.
- Patients not treated with both clopidogrel and aspirin within 24 hours of an MI should not be routinely treated with dual antiplatelet therapy.
- Dual antiplatelet therapy with aspirin and clopidogrel should not be used for longer than 12 months unless another indication for dual antiplatelet therapy exists. After an STEMI, the combination of aspirin and clopidogrel is usually shorter than 12 months.
- Clopidogrel monotherapy may be used in patients intolerant to aspirin.
- Low-dose aspirin and a proton-pump inhibitor are recommended in patients with comorbid dyspepsia.
- After an acute MI, all patients without left ventricular systolic dysfunction or with left ventricular systolic dysfunction should be offered treatment with a β-blocker.
- β-blockers should be continued indefinitely after an acute MI.
- After a proven MI in the past, asymptomatic patients with preserved left ventricular function should not routinely be offered a β-blocker unless they are at risk for further cardiovascular events or other compelling indications exist.
- Patients being treated with warfarin for another indication should continue on warfarin. Those being treated with moderate intensity warfarin (INR 2.0-3.0), at a low risk of bleeding, may be treated with aspirin.
- Calcium-channel blocking agents should not routinely be used to reduce cardiovascular risk after an MI.
- Verapamil or diltiazem may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction in whom β-blockers must be discontinued or in whom β-blockers are contraindicated.
- For patients who are stable after an MI, calcium-channel blockers may be used to treat hypertension and/or angina.
- For patients with heart failure, amlodipine should be used, and verapamil, diltiazem and short-acting dihydropyridine agents should be avoided.
- For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment should be initiated within 3–14 days of the MI, preferably after ACE inhibitor therapy.
- Statins are recommended in patients who have had an MI and should be offered to patients as soon as possible.
- If statin therapy is contraindicated, other lipid-lowering drugs should be considered.

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Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Angina Pectoris
November 10, 2010

I. Overview

Angina pectoris is a condition that is characterized by chest pain, discomfort, or heaviness, which may radiate to the neck, jaw, arm or back. While chest pain is the classic symptom, it may also present as shortness of breath, fatigue or other symptom complexes. Myocardial ischemia develops when there is an imbalance between myocardial oxygen supply and demand. Myocardial ischemia may have various causes. Often it is due to coronary artery disease, which may obstruct the coronary arteries and restrict the flow of oxygenated blood to the myocardium. It may also stem from other conditions which cause abnormal constriction of coronary arteries, or it may occur in situations in which the oxygen-carrying capacity of the blood is reduced.

Angina may be classified as stable, unstable or variant angina. Stable angina is usually precipitated by an increase in myocardial oxygen demand, typically as the result of physical exertion or stress, and the onset of the episodes are usually predictable. Such an episode will typically subside with rest or removal of the stressor, or with minimal use of sublingual nitroglycerin. In unstable angina, ischemia may occur at rest and is primarily caused by reductions in coronary blood flow. Unstable angina is considered an acute coronary syndrome (ACS) and should be treated as a medical emergency. Other types of ACS includes non–ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). The primary causes of reduction in blood flow include the rupture of an atherosclerotic plaque in the coronary artery, thrombus formation and vasoconstriction at the site of the rupture. Variant angina, also known as Prinzmetal's angina, is a form of unstable angina and is caused by a focal vasospasm in a coronary artery.[1-2]

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of angina pectoris are summarized in Table 1.

Table 1. Current Treatment Guidelines for Angina Pectoris

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[3] (2007)
• Lifestyle modifications including smoking cessation, limiting secondhand smoke, weight management, increased physical activity, and dietary changes are recommended in all patients with chronic stable angina. • Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme (ACE) inhibitors and/or β-adrenergic blocking agents (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 mm Hg or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Dietary therapy, physical activity, adding plant sterols/stanols, and consuming omega-3 fatty acids are recommended for all patients to control lipid levels. Low-density lipoprotein cholesterol (LDL-C) levels should be <100 mg/dL, with possible reductions to <70 mg/dL in certain patients. LDL-C lowering medication should be initiated when LDL-C levels are ≥100 mg/dL. • Physical activity of 30-60 minutes 7 days per week is recommended. A medically supervised program such as cardiac rehabilitation is recommended in at-risk patients. • Body mass index should be assessed and maintained between 18.5 kg/m^2 and 24.9 kg/m^2. When waist circumference is ≥35 inches in women and ≥40 inches in men, lifestyle modifications should be initiated and treatment for metabolic syndrome should be considered. • Lifestyle modification and pharmacotherapy are recommended to achieve near-normal hemoglobin A_{1c} (HbA_{1c}) levels in patients with diabetes.

- Aspirin 75-162 mg is recommended in all patients unless contraindicated. Close monitoring is recommended if warfarin is to be used with aspirin and/or clopidogrel.
- ACE inhibitors should be used indefinitely in patients with left ventricular ejection fraction of ≤40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated.
- ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal left ventricular ejection fraction in whom cardiovascular risk factors remain well controlled and revascularization has been performed) unless contraindicated.
- Angiotensin receptor blockers are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a left ventricular ejection fraction of ≤40%.
- Angiotensin receptor blockers may be considered in combination with an ACE inhibitor due to left ventricular systolic dysfunction.
- Aldosterone blockade is recommended 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 left ventricular ejection fraction ≤40% and have either diabetes or heart failure.
- β-blocker therapy is recommended indefinitely in all patients who have had an MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms unless contraindicated.
- All patients with cardiovascular disease should receive an annual influenza vaccine unless contraindicated.
- Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) should be recommended even in mild-to-moderate elevations of LDL-C.
- Use sublingual nitroglycerin (NTG) or NTG spray for immediate relief of angina.
- Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated.
- Immediate-release and short-acting dihydropyridine calcium-channel blocking agents can increase adverse cardiac events and should not be used.
- Long-acting calcium-channel blocking agents or long-acting nitrates may be used with β-blockers if initial treatment is not successful.

European Society of Cardiology (ESC): Management of Stable Angina Pectoris[5] (2006)

Pharmacologic Therapy to Improve Prognosis

- Aspirin (75 daily) is the antithrombotic of choice for most patients unless contraindicated.
- Clopidogrel as an alternative antiplatelet agent in patients with stable angina who cannot take aspirin.
- Dipyridamole is not recommended for antithrombotic therapy in patients with stable angina.
- Statin therapy should be considered in patients with stable CAD and stable angina based on their risk level and the benefit of lowering cholesterol to the normal range. Statin doses shown to reduce morbidity/mortality include simvastatin 40 mg, pravastatin 40 mg, and atorvastatin 10 mg. Dosages should be adjusted as needed to achieve lipid goals. High-dose atorvastatin therapy should be reserved for high-risk patients.
- Other lipid-lowering medications like fibrates, nicotinic acid, and combination products may be added to control lipid levels in patients with severe dyslipidemia.
- ACE inhibitors should be considered in patients with stable angina and comorbid hypertension, diabetes, heart failure, asymptomatic left ventricular dysfunction, and patients who have had an MI. Patients with stable angina who do not have an indication for an ACE inhibitor may be treated with one if the benefits of the agent (possible absolute risk reduction) outweigh the possible side effects.
- β-blockers are recommended as first-line therapy in patients with angina in the absence of contraindications.
- CCBs may be recommended in patients with angina who cannot tolerate β-blockers and who have had an MI and who do not have heart failure.

Symptomatic Treatment and Treatment of Ischemia

- NTG should be prescribed for patients for symptom relief and situational prophylaxis.
- β-blockers should be titrated to full dose. Considerations should be given for 24-hour prophylaxis against ischemia.
- If patients are intolerant to β-blocker therapy, consideration may be given to a CCB or a long-acting nitrate.

Sinus node inhibition may be considered.

- If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. If combination β-blocker and CCB therapy is insufficient, a long-acting nitrate may be substituted for the CCB.

Treatment of Syndrome X

- Recommended therapy includes nitrates, β-blockers, and CCBs alone or in combination.
- Statin therapy is recommended for patients with dyslipidemia.
- ACE inhibitors are recommended in patients with hypertension.
- If pain persists despite the treatment recommendations given above, imipramine and aminophylline may be considered.

Treatment of Vasospastic/Variant Angina

- Treatment with CCBs is recommended. Nitrates may also be used if needed.

American College of Physicians (ACP): Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease[7]
(2004)

Symptomatic Patients

- The following agents are recommended to prevent MI or death and to reduce symptoms: aspirin (clopidogrel may be used in patients intolerant to aspirin), β-blockers, statins, and ACE inhibitors.
- The following agents are recommended to reduce symptoms only: NTG (sublingual or spray), long-acting CCBs or long-acting nitrates (when β-blockers are contraindicated), long-acting CCBs or long-acting nitrates in combination with β-blockers when monotherapy has been unsuccessful.
- The following agents are not recommended to prevent MI or death or to reduce symptoms: dipyridamole and chelation therapy.

Asymptomatic Patients With Evidence Suggesting CAD on Previous Testing

- The following agents should be used to prevent MI and death: aspirin (in patients with a previous MI), β-blockers (in patients with a previous MI), statins (in patients with type 2 diabetes or documented CAD), and an ACE inhibitor (in patients with documented CAD and diabetes, systolic dysfunction, or both).
- The following agents may also be used to prevent MI and death: aspirin in patients who have not had a previous MI, and an ACE inhibitor in patients with diabetes and no contraindications.

American College of Cardiology (ACC)/American Heart Association (AHA): ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (UA/NSTEMI)[4]
(2007)

Early Hospital Care

- Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG every 5 minutes for a total of 3 doses.
- Intravenous NTG is indicated in the first 48 hours after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension.
- Oral β-blocker therapy should be initiated within the first 24 hours for patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk for cardiogenic shock, or 4) other relative contraindications to beta blockade.
- It is reasonable to administer intravenous β-blockers at the time of presentation for hypertension to patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk for cardiogenic shock, or 4) other relative contraindications to beta blockade.
- In patients with continuing or frequently recurring ischemia and in whom β-blockers are contraindicated, a nondihydropyridine calcium-channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction or other contraindications.
- Oral long-acting nondihydropyridine calcium-channel blockers are reasonable for use in patients for recurrent ischemia in the absence of contraindications after β-blockers and nitrates have been fully used.
- The use of extended-release forms of nondihydropyridine calcium-channel blockers instead of a β-blocker

may be considered in patients with UA/NSTEMI.

- Immediate-release dihydropyridine calcium-channel blockers in the presence of adequate beta blockade may be considered in patients with UA/NSTEMI with ongoing ischemic symptoms or hypertension.
- Immediate-release dihydropyridine calcium-channel blockers should not be administered to patients with UA/NSTEMI in the absence of a β-blocker.
- An ACE inhibitor should be administered orally within the first 24 hours to UA/NSTEMI patients with pulmonary congestion or LVEF ≤40% in the absence of hypotension or contraindications.
- An ACE inhibitor administered orally within the first 24 hours of UA/ NSTEMI can be useful in patients without pulmonary congestion or LVEF ≤40% in the absence of hypotension or contraindications.
- An intravenous ACE inhibitor should not be given to patients within the first 24 h of UA/NSTEMI because of the increased risk of hypotension.
- An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of HF or LVEF ≤40%.
- Aspirin should be administered to UA/NSTEMI patients 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 UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance.
- In patients with a history of gastrointestinal bleeding, when ASA 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.
- For patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography with either clopidogrel or an intravenous GP IIb/IIIa inhibitor.
- For patients in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with both clopidogrel and an intravenous GP IIb/IIIa inhibitor.
- For patients in whom an initial conservative strategy is selected, clopidogrel should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month and ideally up to 1 year.
- For patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography.
- Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.

<u>Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge</u>

- Patients treated medically without stenting should be treated indefinitely with aspirin 75-162 mg daily and clopidogrel 75 mg daily for at least one month and ideally for up to 1 year. Clopidogrel can be given instead of aspirin in aspirin-allergic patients or aspirin desensitization may be attempted.
- Patients treated with bare metal stents should be treated with aspirin 162-325 mg daily for at least 1 month followed by 75-162 mg daily indefinitely. Clopidogrel 75 mg daily should be prescribed for at least 1 month and ideally up to 1 year. If the patient is at high risk of bleeding, the clopidogrel should be given for a minimum of 2 weeks. Clopidogrel can be given instead of aspirin in aspirin-allergic patients or aspirin desensitization may be attempted.
- Patients treated with a sirolimus drug eluting stent should be treated with, aspirin 162-325 mg for at least 3 months, and for at least 6 months after a paclitaxel drug-eluting stent. In both cases, the aspirin should be continued indefinitely at 75-162 mg daily. Clopidogrel 75 mg daily should be prescribed for at least 12 months in all patients treated with a drug-eluting stent. Clopidogrel can be given instead of aspirin in aspirin-allergic patients, or aspirin desensitization may be attempted.
- Aspirin may be given at a lower dose of 75-162 mg immediately after stenting in patients who are at a high risk of bleeding or when the prescriber is concerned about the risk of bleeding.
- Patients who have an additional indication for anticoagulation may be treated with warfarin, monitored and adjusted to achieve an international normalized ratio (INR) of 2.0-3.0.
- Warfarin with low-dose aspirin (75-81 mg per day, INR 2.0 to 2.5) or without (INR 2.5 to 3.5) may be reasonable for patients at high coronary artery risk and low bleeding risk who are intolerant of clopidogrel.
- Dipyridamole is not recommended as it has not been shown to be effective.
- β-blockers are recommended in all patients unless otherwise contraindicated. Treatment should be initiated

acutely or within a few days of the event and continued indefinitely. In patients with moderate-to-severe left ventricular failure, β-blockers should be titrated gradually.

- It is reasonable to prescribe β-blockers to low-risk patients (i.e., normal LV function, revascularized, no high-risk features) recovering from UA/NSTEMI in the absence of absolute contraindications.
- ACE inhibitors should be initiated and continued indefinitely in patients with heart failure, left ventricular dysfunction, diabetes, or hypertension unless contraindicated.
- ACE inhibitors are reasonable for all patients, even without left ventricular dysfunction, hypertension, or diabetes unless contraindicated.
- ACE inhibitors are reasonable for patients with heart failure and left ventricular ejection fraction >40%.
- Angiotensin receptor blockers should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and signs of heart failure and left ventricular ejection fraction <40%.
- Combination ACE inhibitor and angiotensin receptor blocker therapy may be considered in patients with persistent symptomatic heart failure and left ventricular ejection fraction <40% despite conventional therapy including an ACE inhibitor or angiotensin receptor blocker alone.
- Aldosterone blockers should be initiated in patients without significant renal dysfunction or hyperkalemia who are receiving therapeutic doses of an ACE inhibitor, have a left ventricular ejection fraction <40%, and either symptomatic heart failure or diabetes.
- Nitroglycerin is recommended to treat ischemic symptoms.
- Calcium-channel blockers are recommended for ischemic symptoms when β-blockers are not successful, contraindicated, or not tolerated.
- Statins are recommended for all patients, including post-revascularization patients, regardless of baseline LDL-C and diet modification.
- LDL-C goals should be <100 mg/dL, with further reductions of <70 mg/dL if desired.
- If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis consist of a fibric acid derivative (fibrate) or niacin before LDL-lowering therapy is recommended. LDL-C should be treated to goal after triglycerides lowering therapy. If possible, it is recommended to achieve a non-high density lipoprotein cholesterol (HDL-C) of <130 mg/dL.
- Plant stanols/sterols and/or viscous fiber are reasonable to further lower LDL-C.
- Omega-3 fatty acids in the form of fish in capsule form (1 g per day) for risk reduction may be reasonable. For the treatment of elevated triglycerides, higher doses (2-4 g per day) may be used for risk reduction.
- Blood pressure control is recommended according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).
- For patients with blood pressure ≥140/90 mm Hg (or ≥130/80 mm Hg for patients with chronic kidney disease or diabetes), it is useful to add blood pressure medication(s) as tolerated, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs such as thiazide diuretics as needed to achieve target blood pressure.
- In patients with diabetes, lifestyle and pharmacological interventions should be initiated to achieve A1C levels of <7%.
- Smoking cessation and reduction of exposure to second-hand smoke are recommended.
- Appropriate weight management and physical activity are recommended.
- Annual influenza vaccination is recommended unless otherwise contraindicated.
- Musculoskeletal pain should be treated with acetaminophen, small doses of narcotics, or non-acetylated salicylates. Therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) may be reasonable if the aforementioned medications do not provide adequate relief.
- NSAIDs with increasing degrees of cyclooxygenase-2 (COX-2) selectivity may be considered only when intolerable discomfort persists despite attempts at therapy with acetaminophen, small doses of narcotics, non-acetylated salicylates, or nonselective NSAIDs.

<u>Variant (Prinzmetal's) Angina</u>

- Treatment with nitrates and CCBs is recommended in patients with variant angina whose coronary angiogram shows no or non-obstructive coronary artery lesions.

<u>Cardiovascular "Syndrome X"</u>

- Nitrates, β-blockers, and calcium-channel blockers (as monotherapy or combination therapy) are recommended in patients with cardiovascular syndrome X.

European Society of Cardiology (ESC): Guidelines for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes (NSTE ACS)[6]
(2007)

Acute Treatment

- β-blockers are recommended in most patients (in the absence of contraindications), especially in patients with hypertension or tachycardia.
- Oral or intravenous nitrates are recommended to relieve symptoms and in the acute management of anginal episodes.
- CCBs may provide additional symptomatic relief in patients already being treated with β-blockers and nitrates. They may also be used in patients who are intolerant to β-blockers and in patients with vasospastic/variant angina. Nondihydropyridine CCBs should not be used unless combined with β-blockers.
- Anticoagulation and antiplatelet agents are recommended in all patients with ACS.
- In a non-urgent situation, fondaparinux is recommended as a first-line anticoagulant. Enoxaparin may be used instead only if the bleeding risk is low.
- During a percutaneous intervention (PCI), the initial anticoagulant should be continued. Additional UFH in the form of a bolus is recommended if fondaparinux is used.
- Anticoagulation may be stopped 24 hours after a PCI, or may be continued up to hospital discharge.
- Aspirin is recommended in all patients without contraindications at an initial dose of 160-325 mg followed by a maintenance dose of 75-100 mg indefinitely.
- A loading dose of clopidogrel is recommended for all patients followed by 75 mg daily for up to 12 months unless the patient is at a high risk of bleeding. Patients undergoing an invasive procedure/PCI may receive an initial loading dose of 600 mg of clopidogrel.
- Clopidogrel may be given to patients who are intolerant to aspirin therapy.
- For patients who are at intermediate-to-high risk, eptifibatide or tirofiban is recommended in addition to antiplatelet agents.
- Patients who are to undergo PCI who were not treated with a GP (glycoprotein) IIb/IIIa inhibitor, abciximab is recommended immediately after angiography.
- GP IIb/IIIa inhibitors must be combined with an anticoagulant.
- Bivalirudin may be used instead of GP IIb/IIIa inhibitors.
- When PCI is planned to be performed within 24 hours, data most strongly supports the use of abciximab.
- NSAIDs should not be administered with aspirin or clopidogrel.
- Clopidogrel may be administered with all statins.
- Interruption of dual antiplatelet therapy with aspirin and clopidogrel during the first 12 months after an 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.

Long-term Management

- Statins are recommended in all ACS patients regardless of cholesterol levels.
- Intensive lipid-lowering therapies (to an LDL-C goal of <70 mg/dL) are recommended.
- β-blockers should be initiated in all patients with left ventricular dysfunction.
- ACE inhibitors are recommended in all patients with left ventricular ejection fraction ≤40% and in patients with diabetes, chronic kidney disease, and hypertension unless otherwise contraindicated.
- ACE inhibitors should be considered for all other patients to prevent the recurrence of ischemia. Agents and doses of proven efficacy are recommended (ramipril and perindopril).
- Angiotensin receptor blockers should be considered in patients intolerant to ACE inhibitors and/or who have heart failure or have had an MI with a left ventricular ejection fraction of ≤40%.
- Aldosterone antagonists should be considered in patients who are already on an ACE inhibitor and β-blocker after an MI, who have a left ventricular ejection fraction of ≤40%, diabetes, or heart failure and who do not have significant renal dysfunction or hyperkalemia.

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Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Heart Failure
November 10, 2010

I. Overview

Heart failure is a progressive clinical syndrome that often results from myocardial muscle dysfunction and associated left ventricular dilation or hypertrophy. It is characterized by elevated cardiac filling pressure and/or inadequate peripheral oxygen delivery.[2] Symptoms of heart failure include fluid retention, shortness of breath and fatigue.[2] The presence and severity of clinical symptoms does not always correlate with the degree of cardiac function. Most patients with heart failure have evidence of left ventricular systolic dysfunction, with or without accompanying diastolic dysfunction.[3] Diastolic heart failure often occurs in the presence of preserved resting left ventricular ejection fraction and is uncommon in younger patients.[3]

The most common system used to classify heart failure was developed by the New York Heart Association (NYHA) and places patients in 1 of 4 functional classes. The American College of Cardiology (ACC) and the American Heart Association (AHA) jointly created stages to describe the progression of heart failure, which complement the NYHA functional classes.[1,4] The NYHA and ACC/AHA classifications are listed in Tables 1 – 2.

Table 1. NYHA Classification of Heart Failure[1,4]

Class	Description
I (Mild)	No limitation of physical activity; ordinary exertion does not cause symptoms.
II (Mild)	Symptoms with ordinary exertion but comfortable at rest.
III (Moderate)	Marked limitation of physical activity; less than ordinary activity causes symptoms but comfortable at rest.
IV (Severe)	Symptoms of heart failure at rest.

Table 2. ACC/AHA Classification of Heart Failure[1,4]

Stage	Description
A	At high risk of developing heart failure due to predisposing conditions, no structural abnormalities or symptoms of heart failure.
B	Structural heart disease but no signs or symptoms of heart failure.
C	Current or prior symptoms of heart failure and structural heart disease.
D	Advanced structural heart disease and heart failure symptoms at rest; requires specialized intervention.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of heart failure are summarized in Table 3.

Table 3. Current Treatment Guidelines for Heart Failure

Heart Failure Society of America (HFSA): 2010 Comprehensive Heart Failure Practice Guideline[2] (2010)
<u>Patients With Risk Factors for Ventricular Remodeling, Cardiac Dysfunction, and Heart Failure</u> • ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. • β-blockers are recommended in patients who have had an MI to reduce mortality, recurrent MI, and prevent heart failure.

Patients With Asymptomatic Heart Failure and Reduced Left Ventricular Ejection Fraction

- ACE inhibitors are recommended for asymptomatic patients with reduced LVEF <40%.
- ARBs are recommended for asymptomatic patients with reduced LVEF who are intolerant of ACE inhibitors from cough or angioedema.
- Routine use of the combination of ACE inhibitors and ARBs for prevention of heart failure is not recommended.
- β-blocker therapy should be considered in asymptomatic patients with reduced LVEF.

Patients With Left Ventricular Systolic Dysfunction

- ACE inhibitors should be used in symptomatic and asymptomatic patients with a LVEF ≤40%.
- ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy.
- Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered.
- ARBs are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency.
- ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy.
- Individual ARBs may be considered as initial therapy rather than ACE inhibitors for patients with heart failure post-MI or chronic heart failure and reduced LVEF.
- β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with an LVEF ≤40%.
- The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40% post-MI and non post-MI.
- β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive agents, including inotropic support. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge in stable patients.
- β-blocker therapy is recommended in the majority of patients with heart failure and reduced LVEF, even if there is concomitant diabetes, chronic obstructive lung disease, or peripheral vascular disease. β-blocker therapy should be used with caution in patients with diabetes with recurrent hypoglycemia, with asthma, or with resting limb ischemia. Considerable caution should be used if β-blockers are initiated in patients with marked bradycardia or marked hypotension. β-blockers are not recommended in patients with asthma with active bronchospasm.
- It is recommended that the dose of β-blocker therapy be titrated slowly. Therapy should continue in most cases during symptomatic exacerbations, though the dose may need to be decreased.
- The routine use of an ARB is not recommended in addition to ACE inhibitor and β-blocker therapy in patients with a recent acute MI and reduced LVEF.
- The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and β-blocker.
- Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics.
- Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker.
- The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia.
- A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced LVEF who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker.

- A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are symptomatic despite optimization of standard therapy.
- Diuretics are recommended to restore volume status in patients with fluid overload/congestive symptoms. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure.
- Torsemide may be considered in patients in whom erratic diuretic effect or absorption is present, particularly those with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics.
- The addition of metolazone or chlorothiazide to loop diuretics should be considered in patients with persistent fluid retention despite high-dose therapy with loop diuretics. Chronic therapy should be avoided due to the potential for electrolyte abnormalities and volume depletion.
- Patients requiring diuretic therapy to treat fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or even discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake.
- Digoxin may be considered to improve symptoms in patients with LVEF ≤40% who have symptomatic heart failure despite therapy with ACE inhibitors and β-blockers.
- Digoxin should be considered for achieving adequate control of the ventricular response to atrial fibrillation in patients with heart failure.
- High doses of digoxin (>0.25 mg/day) for the purpose of rate control are not recommended.
- Use of warfarin (goal INR of 2-3) is recommended for patients with heart failure and chronic paroxysmal, persistent, or long-standing atrial fibrillation or a history of systemic or pulmonary emboli (including stroke or TIA).
- Patients with symptomatic or asymptomatic ischemic cardiomyopathy and recent large anterior MI or a history of a MI with left ventricular thrombus should be treated with warfarin for 3 months following the MI.
- Long-term treatment with an antiplatelet agent, generally aspirin in doses of 75 to 81 mg, is recommended for patients with heart failure due to ischemic cardiomyopathy, whether or not they are receiving ACE inhibitors.
- Warfarin (goal INR 2.0-3.0) and clopidogrel (75 mg) also have prevented vascular events in post-MI patients and may be considered as alternatives to aspirin.
- Routine use of aspirin is not recommended in patients with heart failure without atherosclerotic vascular disease.
- Antiarrhythmic agents, including amiodarone, are not recommended for the primary prevention of sudden death in patients with heart failure.

<u>Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction</u>

- Diuretic treatment is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented.
- In the absence of other specific indications for these drugs, ARBs or ACE inhibitors may be considered in patients with heart failure and preserved LVEF.
- ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. In patients who meet these criteria but are intolerant to ACE inhibitors, ARBs should be considered.
- β-blockers are recommended in patients with heart failure and preserved LVEF who have also had an MI, hypertension, or atrial fibrillation requiring ventricular rate control.
- CCBs should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension.

<u>Patients With Acute Decompensated Heart Failure (ADHF)</u>

- It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally.
- Venous thromboembolism prophylaxis with low dose unfractionated heparin, low molecular weight

heparin, or fondaparinux to prevent proximal deep venous thrombosis and pulmonary embolism is recommended for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and have no contraindication to anticoagulation.

- In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF.
- Intravenous vasodilators (nitroglycerin or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension.
- Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF who have persistent severe heart failure despite aggressive treatment with diuretics and standard oral therapies.
- Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced heart failure characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction, particularly if these patients have marginal systolic blood pressure, have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators.

Patients With Heart Failure and Coronary Artery Disease (CAD)

- Antiplatelet therapy is recommended to reduce vascular events in patients with heart failure and CAD unless contraindicated.
- ACE inhibitors are recommended in all patients with either reduced or preserved LVEF after an MI.
- β-blockers are recommended in patients with reduced LVEF or post-MI.
- ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) in stable hospitalized post-MI patients with LVEF or heart failure.
- Nitrates may be considered in patients who need additional management for symptomatic angina.
- CCBs should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function.

Patients With Heart Failure and Hypertension

- Blood pressure be optimally treated to lower systolic and usually diastolic levels. More than 1 drug may be required. Target resting levels should be <130/<80 mm Hg, if tolerated.
- The use of an ACE inhibitor is recommended.
- The addition of a β-blocker is recommended even if blood pressure is controlled.
- If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine CCB (e.g., amlodipine or felodipine) or other antihypertensive drugs.

Patients With Hypertension and Symptomatic LV Dysfunction With LV Dilation and Low LVEF

- ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) is recommended.
- If blood pressure remains >130/80 mm Hg, a dihydropyridine CCB (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased.

Managing Heart Failure in Special Populations

- Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure and LVEF.
- ACE inhibitor and β-blocker therapy are recommended in all women with symptomatic or asymptomatic heart failure and LV systolic dysfunction. ARBs are recommended for administration to symptomatic and asymptomatic women with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency.
- The combination of hydralazine/isosorbide dinitrate is recommended as standard therapy for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition.
- ACE inhibitor and β-blocker therapy are recommended in all African American patients with symptomatic or asymptomatic heart failure and LV systolic dysfunction. ARBs are recommended as substitute therapy for heart failure in African Americans intolerant of ACE inhibitors.
- A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in

addition to β-blockers and ACE-inhibitors for African Americans with LV systolic dysfunction and NYHA class II-IV heart failure.

American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults[1] (2009)

Patients at Risk for Developing Heart Failure (Stage A)

- Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blocking agents (β-blockers) have been shown to prevent heart failure. The angiotensin receptor blockers (ARBs) losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes and nephropathy.
- Lipid disorders should be treated according to contemporary guidelines.
- Blood sugar in patients with diabetes should be controlled according to contemporary guidelines. ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction (MI), and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension.
- Patients with known atherosclerotic vascular disease should be treated according to current guidelines for secondary prevention.
- ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes, and hypertension with other cardiovascular risk factors.

Patients With Cardiac Structural Abnormalities or Remodeling Who Have Not Developed Heart Failure Symptoms (Stage B)

- β-blockers and ACE inhibitors should be used in all patients with a recent or past history of MI regardless of ejection fraction or presence of heart failure.
- β-blockers and ACE inhibitors should be used in patients who have reduced left ventricular ejection fraction and do not have a history of MI or heart failure.
- ARBs are recommended for patients with reduced left ventricular ejection fraction and a history of an MI if they are intolerant to ACE inhibitors.
- ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy.
- ARBs can be beneficial in patients with low EF and no symptoms of HF who are intolerant of ACEIs.
- Digoxin is not recommended in patients with a low ejection fraction, no heart failure symptoms, and sinus rhythm.
- Calcium-channel blocking agents (CCBs) with negative inotropic effects are not recommended in asymptomatic patients with low ejection fraction after an MI.

Patients With Current or Prior Symptoms of Heart Failure (Stage C)

- Diuretics and salt restriction are recommended in patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction who have evidence of fluid retention.
- ACE inhibitors are recommended in all patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated.
- β-blockers (using 1 of the 3 proven to reduce mortality; i.e., bisoprolol, carvedilol, or extended-release metoprolol) are recommended in all stable patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction unless contraindicated.
- ARBs are recommended in patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction who are intolerant to ACE inhibitors.
- ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced left ventricular ejection fraction.
- The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment.
- Drugs known to adversely affect patients with current or past symptoms of heart failure and reduced left ventricular ejection fraction (nonsteroidal anti-inflammatory drugs (NSAIDs), some CCBs, some antiarrhythmic medications) should be discontinued and avoided if possible.

- Aldosterone antagonists may be beneficial in patients with moderately severe-to-severe symptoms of heart failure with reduced left ventricular ejection fraction, though careful monitoring is required.
- The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African-Americans, with moderate-severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics.
- The addition of a nitrate and hydralazine is reasonable in patients with reduced left ventricular ejection fraction already on an ACE inhibitor and β-blocker and who have persistent symptoms.
- The combination of a nitrate and hydralazine is reasonable in patients who are intolerant to ACE inhibitor and ARB therapy or in whom therapy with one of these agents is contraindicated.
- 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 decreasing hospitalizations in patients with current or past history of heart failure and reduced left ventricular ejection fraction.
- The routine use of a combination of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended.
- CCBs are not recommended as routine treatment for heart failure.

Patients With Heart Failure and Normal Left Ventricular Ejection Fraction

- Systolic and diastolic hypertension should be controlled according to contemporary guidelines.
- Ventricular rate should be controlled in patients with atrial fibrillation.
- Diuretics are recommended to control pulmonary congestion and peripheral edema.
- Restoration and maintenance of normal sinus rhythm may be beneficial in patients with atrial fibrillation and heart failure to control symptoms.
- β-blockers, ARBs, ACE inhibitors, and CCBs may be useful in patients with heart failure and controlled hypertension to improve symptoms.
- The role of digoxin in patients with heart failure and preserved left ventricular ejection fraction is not well established.

Patients With Refractory End-Stage Heart Failure (Stage D)

- Treatment of fluid retention is important.
- Continuous infusion of a positive inotropic agent may be considered for palliative care.
- Routine intermittent infusions of vasoactive and positive inotropic agents are not recommended for patients with refractory end-stage heart failure.

Hospitalized Patients

- For patients admitted with heart failure who have evidence of significant fluid overload, intravenous loop diuretics should be started as soon as possible in the emergency department. If patients are already receiving loop diuretics, the initial intravenous dose should equal or exceed their chronic daily oral dose.
- When diuresis is inadequate to relieve congestion, the diuretic regimen should be intensified using either a higher dose of loop diuretic, addition of a second diuretic, or continuous infusion of a loop diuretic.
- Oral therapies known to improve outcomes (ACE inhibitors, ARBs, β-blockers) should be continued during hospitalization. If not currently treated with these therapies, initiation is recommended prior to hospital discharge.
- Initiation of β-blocker therapy is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators and inotropic agents.
- Intravenous inotropic drugs such as dopamine, dobutamine, or milrinone might be reasonable for those patients presenting with documented severe systolic dysfunction, low blood pressure and evidence of decreased cardiac output with or without congestion in order to maintain systemic perfusion and preserve end-organ performance.

Special Populations

- The combination of a fixed-dose of isosorbide dinitrate and hydralazine to a standard medical regimen for heart failure (including ACE inhibitors and β-blockers) is recommended in order to improve outcomes for patients self-described as African Americans, with NYHA functional class III or IV heart failure.

Patients with Concomitant Disorders

- Nitrates and β-blockers are recommended in patients with heart failure and angina.
- Anticoagulants are recommended in patients with heart failure and atrial fibrillation or a previous thromboembolic event.
- 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.
- Patients with underlying coronary artery disease (CAD) should be prescribed antiplatelet agents.
- Digoxin is reasonable to control ventricular rate in patients with atrial fibrillation and heart failure.
- Amiodarone is a reasonable option to decrease the recurrence of atrial arrhythmias.
- The benefit of enhancing erythropoiesis in patients with heart failure and anemia is not established.
- Class I or II antiarrhythmics are not recommended in patients with heart failure for the prevention of ventricular arrhythmias.
- Antiarrhythmics are not recommended to treat asymptomatic ventricular arrhythmias.

European Society of Cardiology (ESC): Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[3]
(2008)

Pharmacologic Therapy of Chronic Heart Failure

- ACE inhibitors are recommended in patients with LVEF ≤40% irrespective of symptoms.
- β-blockers are recommended for patients with LVEF ≤40% and mild to severe symptoms of heart failure (NYHA class II-IV). Patients with asymptomatic LV systolic dysfunction after MI also have an indication for a β-blocker. Patients should also be receiving ACE inhibitor and/or ARB therapy (and aldosterone antagonist, if indicated).
- β-blockers should usually be initiated in stable patients and only with caution in recently decompensated patients (and only initiated in hospital in these patients).
- Aldosterone antagonist should be considered in all patients with an LVEF ≤35% and severe symptomatic heart failure (NYHA class III-IV) in the absence of hyperkalemia and significant renal dysfunction, unless contraindicated or not tolerated. Patients should also be receiving ACE inhibitor (or ARB) and β-blocker therapy.
- ARBs are recommended in patients with heart failure and LVEF ≤40% as an alternative in patients with mild to severe symptoms (NYHA class II–IV) who are intolerant of an ACE inhibitor or in patients with persistent symptoms (NYHA class II–IV) despite treatment with an ACE inhibitor and β-blocker.
- The combination of hydralazine and isosorbide dinitrate is recommended in symptomatic patients with an LVEF ≤40% as an alternative to an ACE inhibitor or ARB when both of the latter are not tolerated or as add-on therapy to an ACE inhibitor if an ARB or aldosterone antagonist is not tolerated. The evidence is strongest in patients of African-American descent.
- Digoxin may be used to slow a rapid ventricular rate in patients with symptomatic heart failure and atrial fibrillation. It should be used to control heart rate in addition to, or prior to a β-blocker in patients with atrial fibrillation and an LVEF ≤40%.
- Digoxin may be used in patients with sinus rhythm and LVEF ≤40% with mild to severe heart failure symptoms (NYHA class II-IV) in addition to optimal therapy with an ACE inhibitor (or ARB), β-blocker, and aldosterone antagonist, if indicated.
- Diuretics are recommended in patients with heart failure and clinical signs or symptoms of congestion.
- Diuretics cause activation of the renin–angiotensin–aldosterone system in patients with mild symptoms of heart failure and should usually be used in combination with an ACE inhibitor or ARB.
- In general, a loop diuretic will be required in moderate or severe heart failure. A thiazide may be used in combination with loop diuretics for resistant edema, but with caution to avoid dehydration, hypovolemia, hyponatremia, or hypokalemia.

Drugs Used to Treat Cardiovascular Comorbidity in Patients with Chronic Heart Failure

- Warfarin (or an alternative oral anticoagulant) is recommended in patients with heart failure and permanent, persistent, or paroxysmal atrial fibrillation without contraindications to anticoagulation.
- Anticoagulation is also recommended in patients with intracardiac thrombus detected by imaging or evidence of systemic embolism.
- Antiplatelet agents are not as effective as warfarin in reducing the risk of thromboembolism in patients with atrial fibrillation.

- There is no evidence that antiplatelet agents reduce atherosclerotic risk in patients with heart failure.
- In elderly patients with symptomatic chronic heart failure and systolic dysfunction caused by CAD, statin treatment may be considered to reduce cardiovascular hospitalization.

Management of Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (HFPEF)

- No treatment has been shown to reduce morbidity and mortality in patients with HFPEF.
- Diuretics are used to control sodium and water retention and relieve shortness of breath and edema.
- Adequate treatment of hypertension and myocardial ischemia is important, as is control of the ventricular rate in patients with atrial fibrillation.
- Verapamil may improve exercise capacity and symptoms in these patients.

Arrhythmias in Chronic Heart Failure

- A β-blocker or digoxin is recommended to control the heart rate at rest in patients with heart failure and LV dysfunction.
- A combination of digoxin and a β-blocker may be considered to control the heart rate at rest and during exercise.
- In LV systolic dysfunction, digoxin is the recommended initial treatment in hemodynamically unstable patients.
- 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.
- In patients with heart failure and preserved LVEF, a nondihydropyridine calcium-channel antagonist (alone or in combination with digoxin) should be considered to control the heart rate at rest and during exercise.
- Antithrombotic therapy to prevent thromboembolism is recommended for all patients with atrial fibrillation, unless contraindicated.
- In patients with atrial fibrillation at highest risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist to achieve the target INR of 2.0–3.0 is recommended, unless contraindicated.
- Anticoagulation is recommended for patients with >1 moderate risk factor. Such factors include age ≥75 years, hypertension, heart failure, LVEF ≤35%, and diabetes mellitus.
- In patients with heart failure and atrial fibrillation who do not have any additional risk factors, therapy with either aspirin (81–325 mg daily) or a vitamin K antagonist is reasonable for primary prevention of thromboembolism.
- There is no clear evidence that restoring and maintaining sinus rhythm is superior to rate control in reducing morbidity and mortality in patients with persistent atrial fibrillation and heart failure.
- In patients with atrial fibrillation and heart failure and/or depressed LV function, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone.
- Routine, prophylactic use of antiarrhythmic agents in patients with asymptomatic, non-sustained ventricular arrhythmias is not recommended. In heart failure patients, class Ic agents should not be used.
- Amiodarone may be considered as an alternative to ICD to suppress symptomatic ventricular tachycardia in already optimally treated heart failure patients in whom ICD is not an alternative.

Comorbidities and Special Populations

- In hypertensive patients with evidence of LV dysfunction, systolic and diastolic blood pressure should be carefully controlled with a therapeutic target of <140/90 and <130/80 mm Hg in diabetics and high risk patients.
- Antihypertensive regimens based on renin–angiotensin system antagonists (ACE inhibitors or ARBs) are preferable.
- In hypertensive patients with HFPEF, aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended. ACE inhibitors and/or ARBs should be considered the first-line agents.
- ACE inhibitors and ARBs can be useful in patients with diabetes mellitus to decrease the risk of end-organ damage and cardiovascular complications and subsequently risk of heart failure.
- Agents with documented effects on morbidity and mortality such as ACE inhibitors, β-blockers, and ARBs are recommended in patients with co-existing pulmonary disease. The majority of patients with heart failure and COPD can safely tolerate β-blocker therapy. A history of asthma should be considered a contraindication to the use of any β-blocker.

Institute for Clinical Systems Improvement (ICSI): Heart Failure in Adults (2009)[5]
Treatment of Systolic Dysfunction • The cornerstone of therapy 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. ARBs 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. • 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) • 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. 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.

III. References

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Appendix

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacologic Management of Hypertension
November 10, 2010

I. Overview

Hypertension is defined as the persistent elevation of arterial blood pressure. Primary (essential) hypertension has an unknown etiology and accounts for the majority of all cases; whereas, secondary hypertension can be attributable to a specific cause. The most common causes for secondary hypertension are renal parenchymal disease and renal artery stenosis. Hypertension may also be the result of primary hyperaldosteronism, Cushing's syndrome, pheochromocytoma, coarctation of the aorta, pregnancy, estrogen use, or other causes.

Hypertension often coexists with other cardiovascular risk factors, such as tobacco abuse, obesity, physical inactivity, dyslipidemia, diabetes, microalbuminuria, estimated glomerular filtration rate <60 ml/minute, age >55 years for men or >65 years for women, and family history of premature cardiovascular disease.[1] Uncontrolled hypertension can also lead to end-organ damage involving the eye, brain, heart, kidneys and peripheral blood vessels. Therefore, it is imperative to treat hypertension. Antihypertensive therapy has been shown to reduce the incidence of stroke by 35%-40%, myocardial infarction by 20%-25% and heart failure by >50%.[1]

A diagnosis of hypertension is made based upon the average of two or more properly measured systolic and diastolic blood pressure readings that are greater than 140 mm Hg or 90 mm Hg, respectively. The classification of blood pressure in adults according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) is provided in Table 1.[1] Although this classification system is commonly referred to, other guidelines included in this review may classify hypertension by other methods. Where applicable, these classification systems are included in the discussion of the guidelines in which they are presented.

Table 1. JNC 7 Classification of Blood Pressure for Adults Aged 18 Years or Older[1]

Blood Pressure Classification	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 (mm Hg)	and	<80 (mm Hg)
Prehypertension	120-139 (mm Hg)	or	80-89 (mm Hg)
Stage 1 hypertension	140-159 (mm Hg)	or	90-99(mm Hg)
Stage 2 hypertension	≥160 (mm Hg)	or	≥100 (mm Hg)

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines for the diagnosis and management of hypertension are summarized in Table 2.

Table 2. Current Treatment Guidelines for Hypertension

European Society of Hypertension (ESH): Reappraisal of European Guidelines on Hypertension Management[9] (2009)
<u>Blood Pressure Goals of Treatment</u> • It is recommended that SBP be lowered to <140 mm Hg and DBP <90 mm Hg in all hypertensive patients. On the basis of current data, it may be prudent to lower SBP/DBP to 130–139/80–85 mm Hg. <u>Choice of Antihypertensive Drugs</u> • The main benefits of antihypertensive therapy are due to lowering of blood pressure. • Thiazide diuretics (as well as chlorthalidone and indapamide), ACE inhibitors, CCBs, ARBs, and β-

blockers do not differ significantly for their overall ability to reduce blood pressure in hypertension. There is no evidence that these major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction.

- Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice should be avoided.

Combination Therapy

- In the majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs.
- The addition of a drug from another class is recommended, unless the initial drug needs to be withdrawn because of adverse events or lack of efficacy.
- Whenever possible, the use of fixed-dose combinations should be preferred because simplification of treatment carries advantages for compliance.
- Several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an ARB or a CCB, and in recent large-scale trials for the ACE inhibitor/CCB combination. The ARB/CCB combination also appears to be rational and effective. These combinations can be recommended for priority use.
- Despite trial evidence of outcome reduction, the β-blocker/diuretic combination favors the development of diabetes and should be avoided, unless required for other reasons, in predisposed patients. Use of an ACE inhibitor/ARB combination may increase adverse events.
- When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a CCB, and a diuretic.

Antihypertensive Treatment in the Elderly

- Antihypertensive treatment is highly beneficial in the elderly and the choice should not be guided by age.
- Thiazide diuretics, ACE inhibitors, CCBs, ARBs, and β-blockers can be considered for initiation and maintenance of treatment in the elderly.

Antihypertensive Treatment in Diabetic Patients

- All major antihypertensive drug classes protect against cardiovascular complications in diabetic patients. They can all be considered for treatment.
- Combination treatment is commonly needed to effectively lower blood pressure in diabetic patients. A renin–angiotensin receptor blocker should always be included because of the evidence of its protective effect against initiation or progression of nephropathy.

European Society of Hypertension (ESH)/European Society of Cardiology (ESC): Guidelines for the Management of Hypertension[3]
(2007)

- Blood pressure is categorized as follows: (<120 and <80 mm Hg), normal (120-129 and/or 80-84 mm Hg), high normal (130-139 and/or 85-89 mm Hg), grade I hypertension (140-159 and/or 90-99 mm Hg), grade II hypertension (160-179 and/or 100-109 mm Hg), grade III hypertension (≥180 and/or ≥110 mm Hg), and isolated systolic hypertension (≥140 and <90 mm Hg).
- Initiation of drug therapy should be based on blood pressure and total cardiovascular risk.
- The blood pressure goal is <140/90 mm Hg for all hypertensive patients. The goal of treatment for a diabetic patient is blood pressure of <130/80 mm Hg.
- The main benefits of antihypertensive therapy are due to lowering of blood pressure.
- Five major classes of antihypertensive agents (thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists and β-blockers) are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination.
- The choice of drug should depend on several factors, including previous patient response to a class of medications, the effect of a medication on cardiovascular risk according to the patient's cardiovascular profile, presence of compelling indications for certain medications, the presence of disorders which may limit the use of a class of medications, possibility of drug interactions, and side effects.

- Drugs which exert their effects for 24 hours and can be given once daily should be preferred to enhance compliance.
- There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs, CCBs), asymptomatic atherosclerosis (CCBs, ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers, ARBs), angina (CCBs, β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs, aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors, ARBs), permanent atrial fibrillation (β-blockers, non dihydropyridine CCBs), end stage renal disease/proteinuria (ACE inhibitors, ARBs, loop diuretics), metabolic syndrome (ACE inhibitors, ARBs, CCBs), diabetes (ACE inhibitors, ARBs), pregnancy (methyldopa, CCBs, β-blockers), and African American patients (CCBs, diuretics).
- Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk.
- Fixed combination medications can favor compliance and simplify regimens.
- When combining different classes of antihypertensive medications, the following should be considered: medications which have different and complementary mechanisms of action, there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, the combination is likely to be well tolerated.
- Elderly patients may be treated initially with thiazide diuretics, CCBs, ARBs, ACE inhibitors, and β-blockers.
- CCBs, ARBs, and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension.
- β-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes.
- Lipid-lowering therapy, antiplatelet therapy, and glycemic control are recommended in appropriate patients.

National Institute for Health and Clinical Excellence (NICE)/British Hypertension Society (BHS): Hypertension: Management in Adults in Primary Care: Pharmacological Update[4] (2006)

- Drug therapy should be offered to patients with persistent high blood pressure of ≥160/100 mm Hg or those with persistent high blood pressure of >140/90 mm Hg and at high cardiovascular risk (10-year risk of CVD of ≥20% or existing CVD or target organ damage).
- Target blood pressure goal is <140/90 mm Hg.
- Patients with isolated systolic hypertension should be offered the same treatment options as patients with elevated systolic and diastolic blood pressure.
- Initial therapy in patients 55 years of age and older should be a CCB or a thiazide diuretic.
- Initial therapy in patients younger than 55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors.
- If a second medication is required and initial therapy was with a CCB or diuretic, an ACE inhibitor should be added. If initial therapy was with an ACE inhibitor, a CCB or a diuretic should be added.
- If three medications are required, a combination of CCB, ACE inhibitor, and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist.
- If a fourth medication is required, consider a higher dose of a thiazide diuretic or another diuretic, or the addition of a β-blocker or a selective α-blocker.
- β-blockers are generally not preferred for initial therapy for hypertension, though they may be used in younger patients in the case of ACE inhibitor and ARB intolerance, in women of childbearing age, and in patients with an increased sympathetic drive.
- If a β-blocker is used as initial therapy as described above and a second medication is needed, consider adding a CCB instead of a thiazide diuretic (to reduce the risk of developing diabetes).
- Patients who are well-controlled on a β-blocker do not need to be switched from the β-blocker to an alternative agent.
- If a β-blocker is to be discontinued, the dose should be gradually decreased. β-blockers should not be

discontinued in patients who have a compelling indication for β-blockade, including those with angina and those who have had an MI.

National Heart, Lung, and Blood Institute (NHLBI): The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[1] (2004)

- In patients older than 50 years, systolic blood pressure is a more important determinant of cardiovascular disease (CVD) risk than diastolic blood pressure.
- The risk of CVD begins to rise at blood pressures above 115/75 mm Hg and doubles for each incremental increase of 20/10 mm Hg in blood pressure.
- Lifestyle modifications including diet, exercise, alcohol restriction, and weight reduction are recommended in pre-hypertensive patients with systolic blood pressure of 120-139 mm Hg or diastolic blood pressure of 80-89 mm Hg.
- Drug therapy is typically initiated when systolic pressure is ≥140 mm Hg and/or diastolic pressure is ≥90 mm Hg. In patients with diabetes, proteinuric chronic renal failure, or CVD, drug therapy is indicated when systolic pressure is persistently ≥130 mm Hg and/or diastolic pressure is ≥80 mm Hg.
- Thiazide diuretics should be used in most patients with uncomplicated hypertension as monotherapy or combination therapy with drugs from other classes.
- Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-adrenergic blocking agents (β-blockers), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium-channel blocking agents (CCBs). This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications.
- Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from 2 drug classes.
- When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with 2 antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic.
- High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretic, ACE inhibitor, β-blocker, ARB, aldosterone antagonist), post-myocardial infarction (MI) (β-blocker, ACE inhibitor, aldosterone antagonist), high coronary disease risk (diuretic, ACE inhibitor, β-blocker, CCB), diabetes (diuretic, ACE inhibitor, ARB, β-blocker, CCB), chronic kidney disease (ACE inhibitor, ARB), and recurrent stroke prevention (diuretic, ACE inhibitor).
- The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting CCBs may also be used.
- In patients with acute coronary syndromes (ACS) (MI or unstable angina), initial therapy with a β-blocker or an ACE inhibitor is recommended. Other medications may be used as needed for blood pressure control.
- For patients with post-MI, β-blockers, ACE inhibitors, and aldosterone antagonists have been proven to be most beneficial.
- For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists are recommended.
- Thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs are beneficial in reducing CVD and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria.
- Patients with chronic kidney disease often require treatment with 3 or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications.
- African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs,

and β-blockers, compared to CCBs and diuretics. The incidence of ACE inhibitor-induced angioedema is 2-4 times higher in African American patients.

- Pregnant women with hypertension should be treated with β-blockers, methyldopa, or vasodilators.
- Thiazide diuretics are useful in slowing demineralization in osteoporosis.
- β-blockers are useful in the treatment and/or prophylaxis of atrial arrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, and perioperative hypertension.
- CCBs may be useful in Raynaud's syndrome and certain arrhythmias.
- α-Adrenergic blocking agents (α-blockers) may be useful in prostatism.
- Thiazide diuretics should be used cautiously in patients who have gout or a history of significant hyponatremia.
- β-blockers should be used cautiously or avoided in patients with asthma, reactive airways disease, or second or third degree heart block.
- ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
- ACE inhibitors should not be used in patients who have a history of angioedema.
- Aldosterone antagonists and potassium-sparing diuretics can cause hyperkalemia and should not be used in patients whose potassium levels are greater than 5.0 mEq/L.

British Hypertension Society (BHS): Guidelines for Hypertension Management (BHS-IV)[5] (2004)

- Blood pressure is categorized as follows: optimal (<120 and <80 mm Hg), normal (<130 and <85 mm Hg), high normal (130-139 and/or 85-89 mm Hg), grade I hypertension (140-159 and/or 90-99 mm Hg), grade II hypertension (160-179 and/or 100-109 mm Hg), grade III hypertension (≥180 and/or ≥110 mm Hg), and isolated systolic hypertension (grade I: ≥140 and <90 mm Hg, grade II: ≥160 and <90 mm Hg).
- For patients with CVD, other end-organ damage, diabetes mellitus, or an estimated CVD risk of ≥20% over 10 years, drug therapy is recommended when systolic blood pressure is 140-159 mm Hg, diastolic blood pressure is 90-99 mm Hg, or both. Otherwise, drug therapy is recommended when blood pressure is ≥160/100 mm Hg.
- A target blood pressure goal of ≤140/85 mm Hg is recommended for nondiabetic patients and ≤130/80 mm Hg for patients with diabetes, renal impairment or established CVD.

National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI): K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[8] (2004)

- Patients with chronic kidney disease should be considered in the "highest risk" group for CVD and should be treated accordingly.
- Target blood pressure goal should be <130/80 mm Hg.
- All antihypertensives can be used to lower blood pressure in chronic kidney disease. Combination therapy is likely to be necessary to achieve blood pressure goals.
- Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (CCBs, β-blockers), high coronary artery disease risk (diuretics, ACE inhibitors, ARBs, β-blockers, CCBs), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), supraventricular tachycardia (β-blockers, non dihydropyridine CCBs).
- Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB.
- Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or CCB.
- Kidney transplant patients with chronic kidney disease may be treated with CCBs, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.

- If combination therapy is required, separate prescriptions or fixed-dose combinations may be used initially.
- Diuretics should be used in most patients with chronic kidney disease. Thiazide diuretics should be used when glomerular filtration rate ≥30 mL/min/1.73m^2. Loop diuretics should be used when glomerular filtration rate <30 mL/min/1.73m^2. Long-acting diuretics and combinations of diuretics with other antihypertensive agents should be considered to increase patient adherence.
- Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used.

World Health Organization (WHO)/International Society of Hypertension (ISH): 2003 WHO/ISH Statement on Management of Hypertension[2]
(2003)

- Target blood pressure goal is <140/90 mm Hg for low-risk patients with uncomplicated hypertension and <130/80 mm Hg for high-risk patients (e.g., patients with established CVD, diabetes, renal insufficiency).
- A low-dose diuretic should be considered as initial therapy in patients that do not have a compelling indication for a particular drug class.
- If combination therapy is required, a diuretic should generally be a component of this combination, as diuretics should enhance the efficacy of all classes of antihypertensive agents.
- When used as monotherapy, a diuretic or CCB may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients.
- α-Blockers may be useful in patients with prostatism.
- Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine CCBs), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors, and diuretics), left ventricular hypertrophy (ARBs), and cerebrovascular disease (diuretics and ACE inhibitors).

International Society on Hypertension in African Americans: Management of High Blood Pressure in African Americans[7]
(2003)

- Blood pressure goals are <140/90 mm Hg for patients with uncomplicated essential hypertension and <130/80 mm Hg for patients with diabetes, nondiabetic renal disease with significant proteinuria, history of cardiovascular event or stroke, or high risk for coronary artery disease.
- All antihypertensive drug classes are effective in African Americans, though combination therapy is frequently required.
- ACE inhibitors or β-blockers may be less effective in African Americans when used as monotherapy.
- CCBs and thiazide diuretics may be more effective than other drug classes in African Americans.
- In patients with compelling indications, consideration for ACE inhibitors, ARBs, and β-blockers should be equally applied in African American patients.
- Combination therapy is recommended as initial treatment in patients with a systolic blood pressure of >15 mm Hg or a diastolic blood pressure of >10 mm Hg above target blood pressure. The following combinations may be considered: β-blocker plus diuretic, ACE inhibitor plus diuretic, ACE inhibitor plus CCB, or ARB plus diuretic.

American Diabetes Association (ADA): Standards of Medical Care in Diabetes[6]
(2010)

- The blood pressure goal is <130/80 mm Hg for patients with diabetes.
- Patients with systolic blood pressure readings of 130-139 mm Hg or diastolic readings of 80-89 mm Hg should be treated for 3 months with lifestyle modifications. If goal is not achieved in 3 months, pharmacologic treatment is indicated.
- Patients with systolic blood pressure readings of ≥140 mm Hg or diastolic readings of ≥90 mm Hg should be treated with pharmacologic interventions in addition to lifestyle modifications.
- The initial drug therapy regimen should include an ACE inhibitor or an ARB. If additional medications are

needed, a thiazide diuretic may be added if estimated glomerular filtration rate (GFR) is ≥30 ml/min/1.73 m^2 or a loop diuretic for patients whose estimated GFR is <30 ml/min/1.73 m^2.

- Multiple drug therapy is generally required to achieve blood pressure goals.
- During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they can cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review – Intuniv® (guanfacine)
Central Nervous System Agents, Miscellaneous, AHFS Class 289200
November 10, 2010

I. Overview

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common psychiatric disorder that is often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[5-7] The key diagnostic feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent/severe than seen in individuals at a comparable level of development.[5] There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype, and a combined subtype in which both symptoms are displayed.[5] Untreated (or undertreated) ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities.[7]

Extended-release guanfacine was approved by the FDA for the treatment of ADHD in September 2009.[1] Although the exact mechanism of action is unknown, it is thought to stimulate post-synaptic $alpha_{2A}$-adrenergic receptors, which are involved in the modulation of attention and behavior. Guanfacine is not a cerebral stimulant; therefore, it is not a controlled substance and has no known potential for abuse or dependence.[1] This product should not be substituted for immediate-release guanfacine tablets on a mg-mg basis due to differences in their pharmacokinetic parameters.[1]

The most common adverse events reported with extended-release guanfacine are somnolence, sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth and constipation.[1] It should be used with caution in patients at risk for hypotension, bradycardia, heart block or syncope. Heart rate and blood pressure should be monitored prior to initiation of therapy, following dose increases, and periodically while on therapy.[1]

The extended-release guanfacine products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. It is not currently available in a generic formulation. Although immediate-release guanfacine tablets are available generically, these products are not FDA-approved for the treatment of ADHD. The cerebral stimulants/agents used for ADHD class was last reviewed in February 2010.

Table 1. Guanfacine Products Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Guanfacine	extended-release tablet	Intuniv®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cerebral stimulants/agents used for ADHD are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cerebral Stimulants/Agents Used for ADHD

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents[8] (2010)**	Medication Trials • Psychostimulant and non-stimulant medications are FDA-approved therapy in children with ADHD. • Avoid the use of CNS stimulants in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems that could place patients at an increased risk to the sympathomimetic effects of CNS stimulants.

Clinical Guideline	Recommendation(s)
	• All patients should receive a cardiovascular personal and family history, and a physical prior to initiation of stimulants. Medication history or physical exam changes consistent with possible cardiac disease during treatment with stimulant medication may require additional evaluation by a cardiologist. • Two studies show statistically better response to methylphenidate over atomoxetine. • Extended-release guanfacine has not been studied head-to-head with methylphenidate. <u>First-Line Medication Trials</u> • Stimulant medications are considered first-line therapy in children. • Response to one stimulant does not predict response with other stimulant agents. • Atomoxetine is a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or physician. Atomoxetine is a non-controlled substance that may make it preferable in certain clinical situations. <u>Alternative Medications</u> • When adequate stimulant and atomoxetine trials are unsuccessful (due to either poor response or side effects in spite of adjustment), or if associated comorbidity is present, alternative medication trials may be considered. • Second-line medications for ADHD therapy include tricyclic antidepressants (imipramine, desipramine), alpha adrenergic agonist (clonidine) a non-tricyclic antidepressant (bupropion), or immediate-release guanfacine.

National Institute for Health and Clinical Excellence (NICE): **Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People, and Adults**[10] **(2008)**	<u>Treatment for Children and Adolescents with ADHD</u>
	• Methylphenidate, atomoxetine and dexamfetamine are recommended as options for the management of ADHD in children and adolescents.
	• The decision regarding which product to use should be based on the following:
	  o The presence of comorbid conditions
	  o The different adverse effects of the drugs
	  o Specific issues regarding compliance identified for the individual child or adolescent
	  o The potential for drug diversion
	  o The preferences of the child/adolescent and/or his or her parent or guardian.
	• Healthcare professionals should consider the following treatment recommendations:
	  o Methylphenidate for patients with ADHD without significant comorbidities
	  o Methylphenidate for patients with ADHD with comorbid conduct disorder
	  o Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present
	  o Atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate
	• Modified-release preparations should be considered for the following reasons:
	  o Convenience
	  o Improving adherence

Clinical Guideline	Recommendation(s)
	○ Reducing stigma (because the child or young person does not need to take medication at school) ○ Reducing problems schools have in storing and administering controlled drugs ○ Their pharmacokinetic profiles • Immediate-release preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels. <u>Treatment of adults with ADHD</u> • Drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment. • Methylphenidate is recommended as the first-line drug. • If methylphenidate is ineffective or unacceptable, atomoxetine or dexamfetamine can be tried. • Caution should be exercised when prescribing dexamfetamine to those likely to be at risk of stimulant misuse or diversion.
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder**[7] **(2007)**	• Initial pharmacologic therapy should be with an agent approved by the FDA for the treatment of ADHD. This includes dextroamphetamine, methylphenidate (MPH), mixed salts of amphetamine, and atomoxetine. • Stimulants have been shown to be highly effective for the treatment of ADHD in many clinical trials. • Available evidence suggests that both MPH and amphetamines are equally efficacious in the treatment of ADHD. • Immediate-release stimulant medications have the disadvantage that they must be taken two to three times per day to control ADHD symptoms throughout the day. • The long-acting formulations are equally efficacious as immediate-release formulations. • Long-acting formulations may be used as initial therapy. There is no need to titrate to the appropriate dose on short-acting forms and then transfer children to a long-acting form. Short-acting stimulants are often used as initial treatment in small children (<16 kg in weight), for whom there are no long-acting forms in a sufficiently low dose. • Once a medication is initiated, the dose should be titrated every 1 to 3 weeks until the maximum dose is reached, the symptoms of ADHD remit, or side effects prevent further titration. • It is recommended that the patient be in contact with the physician during the titration period and visit the physician after 1 month of therapy to assess effectiveness and determine long-term therapy plans. • Some patients may respond similarly to different stimulant classes; whereas, other patients may preferentially respond to only one class of stimulants. There is no method to predict which stimulant will produce the best response in a given patient. • For the treatment of preschoolers, the available evidence suggests that the titration of stimulants be done slowly and that lower doses may be effective. This may be due to slower metabolism of MPH in preschoolers. • In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants. • Atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although they may produce relatively more nausea or sedation. • Atomoxetine may be considered as a first-line agent in patients with an

Clinical Guideline	Recommendation(s)
	active substance abuse problem, comorbid anxiety, tics, or in those who experience severe side effects while taking stimulants. • It is the choice of the family and the clinician as to which agent should be used for the patient's treatment, and each patient's treatment must be individualized.
British Association of Psychopharmacology: **Evidence-Based Guidelines for the Management of Attention Deficit Hyperactivity Disorder in Adolescents in Transition to Adult Services and in Adults[11] (2006)**	Treatment Recommendations for Children • Proven first-line treatments in children include psychostimulants and atomoxetine. • Second-line treatment options include imipramine and bupropion. • Clonidine and guanfacine may be used as adjunctive treatments. • Qualitative assessments suggest that all agents are more effective than placebo and have similar efficacy; however, there have been few head-to-head comparisons. • The agents are not equivalent in terms of adverse events. • The response to different agents varies between individuals and with different doses. Treatment Recommendations for Adults • Drug treatment needs to be chosen and adapted to best fit the individual, including the patient's preferences and concerns. • Use of methylphenidate in adults has been shown to demonstrate similar drug response effect to that seen in children. • There is limited evidence suggesting that psychostimulants have better efficacy than other treatments for core symptoms. However, amphetamines, methylphenidate and atomoxetine are all effective but not equivalent, since they have different actions and hazards. Abuse Potential • Abuse potential is related to drug action and formulation. Abuse is generally low among patients but it can occur with stimulants. Slow-release preparations of these agents or atomoxetine are preferred for patients with a history of substance abuse, or who are at risk for substance abuse.

American Academy of Pediatrics (AAP): **Clinical Practice Guideline: Treatment of the School-Aged Child With Attention-Deficit Hyperactivity Disorder[9] (2001)**	General Information
	• Upon diagnosis, the clinician should recommend stimulant medications. The three types of stimulants that are recommended are methylphenidate, dextroamphetamine and mixed amphetamine salts.
	• Behavior therapy may be utilized to improve outcomes in children with ADHD.
	Treatment Goals
	• The primary goal of treatment is to maximize function. Desired results include:
	  o Improvements in relationships with parents, siblings, teachers, and peers
	  o Decreased disruptive behaviors
	  o Improved academic performance
	  o Increased independence in self-care or homework
	  o Improved self-esteem
	  o Enhanced safety in the community
	Medication Trials
	• At least 80% of children will respond to one of the stimulants if they are tried in a systematic way. Children who fail to show positive effects or who experience intolerable side effects on one stimulant medication should be tried on another stimulant medication. The reasons for this recommendation include:
	  o Most children who fail to respond to one medication may respond to an alternative stimulant.

Clinical Guideline	Recommendation(s)
	○ Numerous crossover trials indicate efficacy of different stimulants in the same child. ○ Idiosyncratic response to one medication does not dictate a similar response to another. • Children who fail 2 stimulant medications can be tried on a third stimulant medication for the same reason. • When the selected regimen has not met targeted outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions. • If a child fails treatment with at least 3 stimulants, second-line treatments may be considered; these include tricyclic antidepressants, clonidine, and bupropion.

III. Indications

The Food and Drug Administration (FDA)-approved indications for guanfacine 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 Guanfacine[1-4]

Indication	Guanfacine
Treatment of Attention Deficit Hyperactivity Disorder (ADHD)	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of guanfacine are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Guanfacine[1-4]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Elimination (%)	Half-Life (hours)
Guanfacine	Readily absorbed	70	Liver (50)	Renal (50)	18

V. Drug Interactions

Significant drug interactions with guanfacine are listed in Table 5.

Table 5. Significant Drug Interactions with Guanfacine[2]

Generic Name	Significance Level	Interaction	Mechanism
Guanfacine	2	Tizanidine	An additive effect on alpha$_2$-adrenergic receptors by tizanidine and guanfacine may occur. The potential for symptomatic additive hypotension exists when tizanidine is coadministered with guanfacine.

Generic Name	Significance Level	Interaction	Mechanism
Guanfacine	2	Tricyclic antidepressants	Tricyclic antidepressants may antagonize the pharmacodynamic action of guanfacine at the CNS alpha-$_2$ adrenergic receptor. The antihypertensive effect of guanfacine may be decreased by tricyclic antidepressants.

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

VI. Adverse Drug Events

The most common adverse drug events reported with guanfacine are listed in Table 6. Treatment with guanfacine can cause decreases in blood pressure and heart rate. In short-term studies, the maximum mean changes in systolic blood pressure, diastolic blood pressure, and pulse were –5 mm Hg, –3 mm Hg, and –6 bpm, respectively, which were dose dependent.[1] Decreases in blood pressure and heart rate were usually asymptomatic; however, hypotension and bradycardia can occur.[1]

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

Adverse Events	Guanfacine
Cardiovascular	
Atrioventricular block	<2
Bradycardia	<2
Chest pain	<2
Hypertension	2-5
Hypotension	4-10
Orthostatic hypotension	<2
Pallor	<2
Sinus arrhythmia	<2
Syncope	2-5
Central Nervous System	
Agitation	<2
Anxiety	<2
Depression	<2
Dizziness	4-7
Emotional lability	<2
Fatigue	3-15
Headache	19-26
Insomnia	2-5
Interrupted sleep	<2
Irritability	4-6
Lethargy	2-5
Nightmares	<2
Postural dizziness	<2
Seizures	<1
Somnolence/sedation	38-45
Gastrointestinal	
Abdominal pain	7-11
Constipation	1-5
Decreased appetite	2-5
Diarrhea	2-5
Dyspepsia	<2
Nausea	2-7
Stomach discomfort	2-5
Vomiting	9

Adverse Events	Guanfacine
Xerostomia	1-5
Genitourinary	
Enuresis	<2
Increased urinary frequency	<2
Laboratory Test Abnormalities	
ALT increased	<2
Respiratory	
Asthma	<2
Other	
Asthenia	<2
Weight increased	1-7

VII. Dosing and Administration

The usual dosing regimens for guanfacine are listed in Table 7. Following abrupt discontinuation, there were greater mean increases in systolic and diastolic blood pressure and heart rate in healthy young adult volunteers receiving guanfacine compared to placebo; however, these changes generally reflected a return to original baseline.[1] Infrequent, transient elevations in blood pressure above original baseline (i.e., rebound) have been reported to occur upon abrupt discontinuation of guanfacine.[1] To minimize these effects, the dose should generally be tapered in decrements of no more than 1 mg every 3 to 7 days.[1] When reinitiating patients to the previous maintenance dose after two or more missed consecutive doses, physicians should consider titration based on patient tolerability.[1]

Table 7. Usual Dosing Regimens for Guanfacine[1-4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Guanfacine	Safety and efficacy have not been established in adults.	Children 6-17 years of age: <u>Attention-Deficit/ Hyperactivity Disorder:</u> Initial: 1 mg once daily; adjust in increments of no more than 1 mg/week. Maintain the dose within the range of 1-4 mg once daily, depending on clinical response and tolerability. Clinically relevant improvements were observed beginning at doses in the range 0.05-0.08 mg/kg once daily. Efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit. Doses above 4 mg/day have not been studied. In clinical trials, there were dose-related and exposure-	Tablet (ER): 1 mg 2 mg 3 mg 4 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		related risks for several clinically significant adverse reactions. Consideration should be given to dosing guanfacine on a mg/kg basis, in order to balance the potential benefits and risks of treatment.	

ER=extended-release

VIII. Effectiveness

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

Table 8. Comparative Clinical Trials with Guanfacine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Biederman et al.[12] (2008) Guanfacine extended-release (GXR) 2 to 4 mg once daily vs placebo	RCT, DB, MC, PC Patients 6 to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=345 8 weeks	Primary: ADHD Rating Scale IV (ADHD-RS-IV) total score observed during the last treatment week of the dosage escalation period (weeks 1–5) Secondary: CGI-S, CGI-I, PGA, CPRS-R, and CTRS-R observed during the last treatment week of the dosage escalation period (weeks 1–5)	Primary: The mean reduction in ADHD-RS-IV score at end point across all GXR groups was -16.7 compared with -8.9 for placebo. Placebo-adjusted LS mean end point changes from baseline in the GXR 2 mg, 3 mg, and 4 mg groups were -7.70 (P=0.0002), -7.95 (P=0.0001), and -10.39 (P<0.0001), respectively. Mean changes from baseline in hyperactivity/impulsivity in the placebo and GXR 2 mg, 3 mg, and 4 mg groups were -3.51, -7.33 (P=0.0002 vs placebo), -7.32 (P=0.0002 vs placebo), and -9.31, (P<0.0001 vs placebo) respectively. Mean changes from baseline in inattentiveness were -4.92, -8.7 (P=0.0011 vs placebo), -9.11 (P=0.0006 vs placebo), and -9.44 (P=0.0002 vs placebo), respectively. Secondary: Significant improvement in CGI-I scores at end point was shown in 25.64%, 55.95%, 50.00%, and 55.56% of patients in the placebo and GXR 2 mg, 3 mg, and 4 mg groups, respectively. Improvement in CGI-I scores was significant in the GXR 2 mg group compared with the placebo group by week 2 (P=0.0194) and in all GXR groups by week 3 continuing through week 5 (P<0.05). Significant improvement in PGA scores at end point was shown in 23.08%, 62.12%, 50.82%, and 66.10% of patients in the placebo and GXR 2 mg, 3 mg, and 4 mg groups, respectively. On the CPRS-R, placebo-adjusted LS mean day total end point changes from baseline were -6.55 in the 2 mg group (P=0.0448), -7.36 in the 3 mg group (P=0.0242), and -12.70 in the 4 mg group (P<0.0001). On the CTRS-R, placebo-adjusted LS mean day total end point changes from baseline were -11.57 (P<0.0001), -13.48 (P<0.0001), and -12.53

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.0001), for the 2 mg, 3 mg, and 4 mg doses, respectively. The most commonly reported treatment-emergent adverse events (TEAEs) were somnolence, fatigue, upper abdominal pain and sedation. The incidence of somnolence in patients who were receiving GXR 1 mg, 2 mg, 3 mg, and 4 mg doses was 12.7%, 11.4%, 20.9%, and 17.5%, respectively. Systolic BP (SBP), diastolic BP (DBP), and pulse rate decreased as GXR dosages increased, then increased as dosages stabilized and tapered down. The greatest mean changes from baseline in SBP and DBP for patients who were receiving GXR 2 mg, 3 mg, and 4 mg doses were -7.0 mm Hg (week 3) and -3.8 mm Hg (week 2), -7.0 mm Hg (week 3) and -4.7 mm Hg (weeks 3 and 5), and -10.1 mm Hg (week 4) and -7.1 mm Hg (week 4), respectively. The greatest mean changes from baseline in pulse rate for patients who were receiving GXR 2 mg, 3 mg, and 4 mg doses were -5.7 beats per minute (bpm; week 3), -8.1 bpm (week 3), and -8.0 bpm (week 4), respectively. Mean changes in height and weight from baseline to end point were not significant across the treatment groups.
Biederman et al.[13] (2008) Guanfacine extended-release (GXR) 2 to 4 mg once daily	OL, ES Patients 6 to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=240 24 months	Primary: Safety Secondary: ADHD-RS-IV, PGA, CHQ-PF50	Primary: Somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%) were the most frequently reported adverse events (AEs). Changes from baseline to endpoint in systolic blood pressure, diastolic blood pressure, and pulse rate were -0.8 mm Hg, -0.4 mm Hg, and -1.9 beats per minute (bpm), respectively. Mean changes in pulse rate and QRS intervals were generally unchanged across study visits. Hypotension was reported in 2.9% of patients and bradycardia was reported in 2.1% of patients. There were no unexpected changes in mean height or weight. Approximately 7% of patients reported weight increase possibly or probably related to study drug. Weight decrease was not reported. Appetite increase was reported by 2.1% of patients, appetite decrease by 3.3% of patients, and anorexia by 0.8% of patients. Secondary: The mean ADHD-RS-IV total score was significantly reduced from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				baseline to endpoint (-18.1; P<0.001 vs baseline). Mean reductions in ADHD-RS-IV scores were significant for both the inattention (-9.5; P<0.001 vs baseline) and the hyperactivity/impulsivity (-8.5; P<0.001 vs baseline) subscales. For PGA scores, 58.6% of patients were 'improved' at endpoint compared with baseline of the preceding study. For the CHQ-PF50, physical summary scores did not change significantly from baseline to endpoint overall or in any dose or age group.
Sallee et al.[16] (2009) Guanfacine extended-release (GXR) 1 to 4 mg once daily vs placebo	RCT, DB, MC, PC Patients 6 to 17 years of age with ADHD and a baseline score of 24 on the ADHD Rating Scale-IV	N=324 9 weeks	Primary: ADHD Rating Scale IV (ADHD-RS-IV) total score Secondary: CPRS-R, CGI-I, and PGA	Primary: The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all GXR dose groups was -19.6 compared with -12.2 for placebo. The placebo-adjusted mean endpoint changes from baseline were -6.75 (P=0.0041), -5.41 (P=0.0176), -7.34 (P=0.0016), and -7.88 (P=0.0006) in the GXR 1 mg, 2 mg, 3 mg, and 4 mg groups, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were: -4.2 (P=0.002), -3.0 P=0.02), -3.5 (P=0.007), and -4.0 (P=0.002) for GXR 1 mg, 2 mg, 3 mg, and 4 mg, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of hyperactivity/impulsivity were: -2.7 (P=0.028), -2.5 (P=0.03), -3.9 (P=0.001), and -4.0 (P=0.0008) for GXR 1 mg, 2 mg, 3 mg, and 4 mg, respectively. Secondary: Using placebo-adjusted LS mean differences in change from baseline at endpoint in CPRS-R total scores, the 4 mg GXR dose demonstrated significant efficacy at 8 hours (-10.2; P=0.004) and 12 hours (-7.5; P=0.04). The 3 mg GXR dosage group demonstrated significant improvements in CPRS-R results at 8 (-11.8; P=0.002), 12 (-9.6; P=0.01), and 14 hours (-9.8; P=0.0156) postdose. The 2 mg GXR dosage group demonstrated significant improvements in CPRS-R scores at 8 hours (-9.0; P=0.01) postdose. For the 1 mg GXR dosage group, the placebo-adjusted LS mean differences in CPRS-R at 8, 12, 14, and 24 hours were -12.8

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.0004), -11.4 (P=0.002), -10.4 (P=0.0077), and -8.9 (P=0.02), respectively. Based on CGI-I scores, the percentages of the patients showing clinical improvement were 30% (placebo), 54% (GXR 1 mg; P=0.007 vs placebo), 43% (GXR 2 mg; P=0.1404 vs placebo), 55% (GXR 3 mg; P=0.006 vs placebo), and 56% (GXR 4 mg; P=0.004 vs placebo). Improvements in PGA scores were 30% (placebo), 51% (GXR 1 mg; P=0.030 vs placebo), 36% (GXR 2 mg; P=0.4982 vs placebo), 62% (GXR 3 mg; P=0.002 vs placebo), and 57% (GXR 4 mg; P=0.0063 vs placebo). Mild to moderate treatment-emergent adverse events (TEAEs) in patients taking GXR were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. There was no significant differences in sleepiness between the patients taking placebo and GXR. GXR was not associated with abnormal changes in height or weight. Systolic BP (SBP), diastolic BP (DBP), and pulse rate (PR) decreased as the GXR dose increased and then increased during dose maintenance and tapering. The range of mean changes from baseline for seated SBP for the placebo group was -1.30 to -0.48 mm Hg and -7.38 to 0.54 mm Hg for the GXR randomized dose groups.
Sallee et al.[17] (2009) Guanfacine extended-release (GXR) 1 to 4 mg once daily	OL, ES Patients 6 to 17 years of age with ADHD and a baseline score of 24 on the ADHD Rating Scale-IV	N=257 24 months	Primary: Safety and efficacy (ADHD-RS-IV, CPRS-R, CGI-I, CHQ-PF50, CTRS-R, and PGA)	Primary: Somnolence (30.5%), headache (24.3%), upper respiratory tract infection (17.8%), nasopharyngitis (14.3%), fatigue (13.9%), upper abdominal pain (12.7%) and sedation (11.2%) were the most frequently reported adverse events (AEs). The majority of somnolence, sedation, or fatigue events were moderate or mild in severity and resolved by end of treatment. Hypotension was reported in 5.0% of patients. Decreased diastolic blood pressure (DBP) was found in 3.5% of patients, decreased blood pressure in 2.7% of patients, and decreased systolic BP in 2.3% of patients. Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were among the most common treatment-emergent AEs that differed in the subgroup co-administered psychostimulants relative to monotherapy or the overall safety population.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Mean changes in ADHD-RS-IV total score from baseline to end point showed significant improvement: overall, -20.1 (P<0.001), and for all GXR dose groups, -23.8, -22.5, -20.0, and -18.4 for the 1 mg, 2 mg, 3 mg, and 4 mg dose groups, respectively (P<0.001 for each). CPRS-R mean changes from baseline to end point were statistically significant in the overall treatment group (-18.2; P<0.001). The overall mean change from baseline demonstrated significant improvement in CPRS-R scores at each postdose assessment (P<0.001). Investigator-rated CGI-I scores at end point showed that investigators rated the majority of patients very much improved (29.3%) or much improved (28.8%). For the PGA, 59.7% of patients were rated as very much or much improved at end point. Mean changes in CHQ-PF50 Physical Summary Scores from baseline to end point were not statistically significant. CHQ-PF50 Psychosocial Summary Scores demonstrated significant improvement from baseline to end point for the overall full analysis set (P<0.001).
Connor et al.[18] (2010) Guanfacine extended-release (XR) 1 to 4 mg once daily vs placebo	RCT, DB, PC, MC Patients 6–12 years of age with a diagnosis of attention-deficit hyperactivity disorder (ADHD) and the presence of oppositional symptoms	N=217 9 weeks	Primary: Change from baseline to endpoint in the oppositional subscale of the CPRS-R:L Secondary: Change in ADHD-RS-IV total score and safety	Primary: The mean change from baseline in the oppositional subscale of the CPRS-R:L was -10.9 for those receiving guanfacine XR and -6.8 for those receiving placebo (P<0.001). The mean percentage reductions from baseline were 56.3% with guanfacine XR and 33.4% with placebo (P<0.001). Secondary: The mean decrease from baseline to endpoint in ADHD-RS-IV total score was 23.8 points for guanfacine XR compared with 11.5 for placebo (P<0.001). The mean percentage reductions from baseline were 56.7% with guanfacine XR and 26.5% with placebo (P<0.001). Adverse events (AEs) were reported in 84.6% of those receiving guanfacine XR group and 60.3% of those receiving placebo. Treatment-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				emergent AEs (TEAEs) occurred more frequently with guanfacine XR than with placebo (83.8% vs 57.7%, respectively). The most common TEAEs in the guanfacine XR group were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%) and fatigue (11.0%).
Spencer et al.[15] (2009) Guanfacine extended-release (GXR) 1 to 4 mg once daily added to existing stimulant therapy	MC, OL Patients 6 to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive-impulsive subtype) and who were on a stable regimen of either methylphenidate (MPH) or amphetamine (AMP) for at least 1 month with suboptimal control of ADHD symptoms	N=75 9 weeks	Primary: Safety and efficacy (ADHD-RS-IV, CPRS-R, CGI-I, CGI-S, CHQ-PF50, and PGA)	Primary: The most common treatment-related adverse events (AEs) were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Most AEs were mild to moderate in severity. The incidences of the TEAEs were comparable between both psychostimulant subgroups except for fatigue (28.6% in the GXR+MPH subgroup vs 18.2% in the GXR+AMP subgroup) and irritability (14.3% in the GXR+MPH subgroup vs 33.3% in the GXR+AMP subgroup). Twenty subjects has a decrease in blood pressure judged to be of clinical interest. Twelve subjects exhibited orthostatic blood pressure decreases. None of the subjects with blood pressure decreases reported syncope or lightheadedness. At baseline, the mean Pediatric Daytime Sleepiness Scale (PDSS) score was 15.0. Decreases were observed at visit 6 (-4.8) and end point (-3.1). During treatment, there was an increase from screening in the number of subjects reporting clinically significant dullness, tiredness, and listlessness on the Pittsburgh Side Effects Rating Scale (PSERS). There was a decrease in the number of subjects with clinically significant loss of appetite and trouble sleeping. The psychostimulant subgroups were generally comparable. Significant decreases from baseline (psychostimulant only) to end point in ADHD-RS-IV total score were observed overall and in both psychostimulant combination subgroups, indicating improvement in ADHD symptoms (overall -16.1, GXR+MPH group -17.8, GXR+AMP group -13.8; P<0.0001 for all). The mean percentage reduction from baseline to end point in ADHD-RS-IV score overall was 56.0%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Improvement was significant for the mean day CPRS-R total score (-19.8, P<0.0001), as well as for all three time points (-23.2 at 12 hours postdose, -18.5 at 14 hours postdose, and -17.8 at 24 hours postdose; all P<0.0001). The percentage of subjects showing improvement at end point on the CGI was 73.0%. On the PGA, 84.1% of subjects showed improvement. No significant improvement occurred at end point in the CHQ-PF50 physical summary score. Mean improvement for the CHQ-PF50 psychosocial score was 10.2 (P<0.0001).
Faraone et al.[14] (2010) Guanfacine extended-release (GXR) 1 to 4 mg once daily	MA Patients 6 to 17 years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype)	N=813 6 to 9 weeks	Primary: Predictors of efficacy and sedation using various models	Primary: <u>Actual Dose Model</u> The presence or absence of ADHD symptoms was influenced by the actual doses of medication received by the participants (P=0.006). In participants with residual ADHD symptoms, greater total ADHD-RS symptom scores were significantly related to shorter treatment duration (P<0.001) and higher baseline total ADHD-RS symptom scores (P<0.001). The only significant influence on the frequency of sedation-related AEs was treatment duration (P=0.034). <u>mg/kg Dose Model</u> The presence or absence of ADHD symptoms was significantly influenced by the dose of medication received by the participant as expressed in mg/kg (P=0.001). Treatment duration (P<0.001) and baseline total ADHD-RS symptom scores (P<0.001) were predictors of weekly total ADHD-RS symptom scores. The only significant influence on the frequency of sedation-related AEs was treatment duration (P=0.034). <u>Titration Rate Dose Model</u> The presence or absence of ADHD symptoms was significantly influenced by the titrated dose of medication received by the participant (P=0.005). The number of symptoms was significantly influenced by treatment duration (P<0.001) and baseline total ADHD-RS scores (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The only significant influence on the frequency of sedation-related AEs was treatment duration (P=0.034).

Study abbreviations: DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial
Miscellaneous abbreviations: ADHD=Attention-Deficit/Hyperactivity Disorder, ADHD-RS-IV=ADHD Rating Scale IV, CGI-I=Clinical Global Impression of Improvement, CGI-S=Clinical Global Impression of Severity, CHQ-PF50=Child Health Questionnaire-Parent Form 50, CPRSR=Conners' Parent Rating Scale–Revised: Short Form, CPRS-R:L=Conners' Parent Rating Scale-Revised: Long Form, CTRS-R=Conners' Teacher Rating Scale–Revised: Short Form, PGA=Parent's Global Assessment

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 Guanfacine

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Guanfacine	extended-release tablet	Intuniv®	$$$$	N/A

N/A=Not available

X. Conclusions

Extended-release guanfacine is FDA-approved for the treatment of ADHD.[1] Although the exact mechanism of action is unknown, it is thought to stimulate post-synaptic $alpha_{2A}$-adrenergic receptors, which are involved in the modulation of attention and behavior. Guanfacine is not a cerebral stimulant; therefore, it is not a controlled substance and has no known potential for abuse or dependence.[1] This product should not be substituted for immediate-release guanfacine tablets on a mg-mg basis due to differences in their pharmacokinetic parameters.[1] Extended-release guanfacine tablets are not available in a generic formulation. Although immediate-release guanfacine tablets are available generically, these products are not FDA-approved for the treatment of ADHD.

Guidelines recommend the use of cerebral stimulants for the initial treatment of children and adolescents with ADHD.[7-8,10-11] Atomoxetine is recommended for patients with comorbid anxiety disorders, tics, sleep disorders, substance abuse, stimulant failure, or adverse events with stimulants. Immediate-release guanfacine is recommended as an alternative treatment option for ADHD.[8,11] It should be noted that extended-release guanfacine was approved by the FDA after the publication of the majority of these clinical guidelines.

There are several factors to take into consideration when selecting a pharmacologic agent for the treatment of children and adolescents with ADHD.[7-11] This includes the presence of comorbid conditions, patient/family preference, storage/administration at school, history of substance abuse, drug diversion, pharmacokinetics and adverse events. The advantage of a once-daily formulation is that medication does not need to be taken during school hours, as is the case with immediate-release formulations. Administration of medications during school hours, especially Schedule II controlled substances, can be difficult since the medication must be administered by a licensed school nurse. Extended-release guanfacine is not a controlled substance, which may make it preferable to cerebral stimulants in certain situations.

The efficacy of extended-release guanfacine in the treatment of children and adolescents with ADHD is based on the results of three (8 to 9 week) placebo-controlled studies.[12,16,18] The mean reductions in Attention-Deficit/Hyperactivity Disorder Rating Scale IV total scores, as well as placebo-adjusted changes from baseline, were significantly greater with guanfacine compared to placebo. There were also improvements in hyperactivity/impulsivity and inattentiveness subscales, oppositional subscale, Clinical Global Impression of Improvement, Parent's Global Assessment, Conners' Parent Rating Scale–Revised, and Conners' Teacher Rating Scale–Revised assessments compared with placebo. Two long-term, open-label, non-comparative studies have also demonstrated that extended-release guanfacine is safe and effective when administered to children and adolescents for up to 24 months.[13,17] Extended-release guanfacine was also found to be safe and effective when added to existing cerebral stimulant therapy.[15] There were no published studies found in the medical literature that directly compared extended-release guanfacine to cerebral stimulants or atomoxetine. Efficacy beyond 9 weeks and safety beyond 2 years of treatment have not been established.[1] Maintenance treatment has not been systematically evaluated, and patients who are continued on longer-term treatment require periodic reassessment.[1]

The most common adverse events reported with extended-release guanfacine are somnolence, sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth and constipation.[1] It should be used with caution in patients at risk for hypotension, bradycardia, heart block or syncope. Heart rate and blood pressure should be monitored prior to initiation of therapy, following dose increases, and periodically while on therapy.[1]

At this time, there is insufficient evidence to conclude that extended-release guanfacine offers a significant clinical advantage over other alternatives in general use. It should be available as adjunctive therapy through the medical justification portion of the prior authorization process.

XI. Recommendations

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

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review – Ulesfia® (benzyl alcohol)
Scabicides and Pediculicides, AHFS Class 840412
November 10, 2010

I. Overview

Pediculosis is a transmissible skin infection, which is caused by three different kinds of lice depending on the location: head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*), and pubic region (*Phthirus pubis*).[5] Pediculosis capitis (head lice) is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[5] Head lice infestation is most common in children and is not a sign of poor hygiene.[7] Transmission primarily occurs by direct head-to-head contact with hair of infested people. Head lice do not spread any diseases; therefore, they are not considered a health hazard.[7] The goal of therapy is to eradicate the parasite and topical pediculicides are the treatment of choice.[5-9]

Benzyl alcohol lotion was approved by the FDA in April 2009 for the topical treatment of head lice infestation in patients 6 months of age and older.[4] The lotion is applied to dry hair using enough to completely saturate the scalp/hair and is then rinsed off after 10 minutes. Benzyl alcohol inhibits lice from closing their respiratory spiracles, which causes the lice to asphyxiate; however, it is not ovicidal.[4] Therefore, a second treatment is required after 7 days to eradicate any lice that may have hatched since the first application.

The benzyl alcohol products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Benzyl alcohol lotion is not available in a generic formulation. The skin and mucous membrane scabicides and pediculicides class was last reviewed in May 2009.

Table 1. Benzyl Alcohol Products Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Benzyl alcohol	lotion	Ulesfia®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the scabicides and pediculicides are summarized in Table 2.

Table 2. Treatment Guidelines Using the Scabicides and Pediculicides

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics (AAP): **Clinical Report – Head Lice[9] (2010)**	• No healthy child should be excluded from or allowed to miss school time because of head lice. No-nit policies for return to school should be abandoned. • Unless resistance to these products has been proven in the community, 1% permethrin or pyrethrins can be used for treatment of active infestations. • Instructions on the proper use of products should be carefully communicated. Because current products are not completely ovicidal, applying the product at least twice, at proper intervals, is recommended if permethrin or pyrethrin products are used or if live lice are seen after malathion therapy. Manual removal of nits immediately after treatment with a pediculicide is not necessary to prevent spread. In the school setting, nit removal may be considered to decrease diagnostic confusion. • If resistance to available OTC products has been proven in the

Clinical Guideline	Recommendation(s)
	community, if the patient is too young, or if parents do not wish to use a pediculicide, consider recommending "wet-combing" or an occlusive method (such as petroleum jelly or Cetaphil), with emphasis on careful technique, and repeating for at least 2 weekly cycles. • Benzyl alcohol 5% can be used for children older than 6 months, or malathion 0.5% can be used for children 2 years old or older, in areas where resistance to permethrin or pyrethrins has been demonstrated or for a patient with a documented infestation that has failed to respond to appropriately administered therapy with permethrin or pyrethrins. • New products should be evaluated for safety and effectiveness.
Sanford Guide to Antimicrobial Therapy[8] (2010)	Head lice • Primary: permethrin 1% lotion applied for 10 minutes and repeated in 9-10 days OR malathion 0.5% lotion applied for 8-12 hours and repeated in 7-9 days • Alternative: Ivermectin 200 mcg/kg orally once with a total of 3 doses administered at 7 day intervals • Due to potential neurotoxicity and risk of aplastic anemia, lindane is not recommended.
American Academy of Pediatrics (AAP) Red Book: **Pediculosis Capitis (Head Lice)[7] (2009)**	• Malathion, permethrin, pyrethrin-based products, crotamiton, oral trimethoprim-sulfamethoxazole and oral ivermectin are effective for treating head lice. • Therapy could be started with over-the-counter 1% permethrin, but resistance approaching 50% in the United States has been documented. • For treatment failures with permethrin or pyrethrins, malathion should be used. • When lice are resistant to all topical agents, ivermectin may be used, although it is not approved by the FDA as a pediculicide. • No drug is truly ovicidal, but of the available topical agents, only malathion has ovicidal activity. • Safety is a major concern with pediculicides, because the infestation itself does not present a risk to the host. • Pediculicides usually require more than one application. Ideally, retreatment should occur after the eggs that are present at the time of initial treatment have hatched, but before any new eggs have been produced. • Data are lacking to determine whether suffocation of lice by application of some occlusive agents, such as petroleum jelly, olive oil, butter, or fat-containing mayonnaise, is effective as a method of treatment. • Because pediculicides kill lice shortly after application, detection of living lice on scalp inspection 24 hours or more after treatment suggests incorrect use of pediculicide, hatching of lice after treatment, reinfestation, or resistance to therapy. • Immediate retreatment with a different pediculicide followed by a second application 9 to 10 days later is recommended. • Itching or mild burning of the scalp caused by inflammation of the skin in response to topical therapeutic agents can persist for many days after lice are killed and is not a reason for retreatment. Topical corticosteroid and oral antihistamine agents may be beneficial for relieving these signs and symptoms. • Manual removal of nits after successful treatment with a pediculicide is helpful, because none of the pediculicides are 100% ovicidal.

III. Indications

The Food and Drug Administration (FDA)-approved indications for benzyl alcohol 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 Benzyl Alcohol[1-4]

Indication	Benzyl Alcohol
Topical treatment of head lice infestation in patients 6 months of age and older	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of benzyl alcohol are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Benzyl Alcohol[1-4]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Elimination (%)	Half-Life (hours)
Benzyl alcohol	Not reported	Not reported	Not reported	Not reported	Not reported

V. Drug Interactions

Drug interaction studies were not conducted with benzyl alcohol lotion.[4]

VI. Adverse Drug Events

The most common adverse drug events reported with benzyl alcohol are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with Benzyl Alcohol[1-4]

Adverse Events	Benzyl Alcohol
Application site anesthesia and hypoesthesia	2
Application site dermatitis	<1
Application site dryness	<1
Application site excoriation	<1
Application site irritation	2
Dandruff	<1
Erythema	10
Excoriation	<1
Ocular irritation	6
Pain	1
Paraesthesia	<1
Pruritus	12
Pyoderma	7
Rash	<1
Skin exfoliation	<1
Thermal burn	<1

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for benzyl alcohol are listed in Table 6.

Table 6. Usual Dosing Regimens for Benzyl Alcohol[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Benzyl alcohol	Apply to dry hair, using enough to completely saturate the scalp and hair. Rinse off with water after 10 minutes. Repeat treatment in 7 days.	Children ≥6 months of age: Apply to dry hair, using enough to completely saturate the scalp and hair. Rinse off with water after 10 minutes. Repeat treatment in 7 days.	Lotion: 5%

VIII. Effectiveness

Two multicenter, randomized, double-blind, vehicle-controlled studies were conducted with benzyl alcohol as described in the package insert.[4] A total of 250 patients ≥6 months of age with an active head lice infestation received two 10-minute treatments with benzyl alcohol, which were applied one week apart. The primary efficacy endpoint was the proportion of patients who were free of live lice 14 days after the final treatment. Patients with live lice present at any time after first treatment were considered to be treatment failures. In the first study, 76.2% of patients receiving benzyl alcohol were free of live lice compared to 4.8% of patients receiving vehicle. In the second study, 75.0% of patients receiving benzyl alcohol were free of live lice compared to 26.2% of patients receiving vehicle.

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 7. Relative Cost of Benzyl Alcohol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Benzyl alcohol	lotion	Ulesfia®	$$	N/A

N/A=Not available

X. Conclusions

Head lice infestation is most common in children with transmission primarily occurring by direct head-to-head contact with hair of infested people.[7] Head lice do not spread any diseases; therefore, they are not considered a health hazard.[7] The goal of therapy is to eradicate the parasite and topical pediculicides are the treatment of choice.[5-9] Benzyl alcohol lotion was approved by the FDA in April 2009 for the topical treatment of head lice infestation in patients ≥6 months of age.[4] It is not currently available in a generic formulation.

None of the available pediculicides are completely ovicidal, which requires applying the product at least twice at proper intervals.[9] Resistance has also been reported with lindane, pyrethrins and permethrin.[6] The American Academy of Pediatrics recommends the use of permethrin (1%) or pyrethrins as initial therapy, unless resistance to these products has been proven in the community.[7,9] Benzyl alcohol (5%) or malathion (0.5%) can be used in areas where resistance to permethrin or pyrethrins has been demonstrated, or for a patient who has failed to respond to either of these agents.

There were no published studies found in the medical literature evaluating the efficacy and safety of benzyl alcohol; however, according to the package insert, two phase III studies have been conducted.[4] Benzyl alcohol eliminated all live lice in 76.2% and 75% of patients compared to 4.8% and 26.2% of patients receiving vehicle alone.

At this time, there is insufficient evidence to conclude that benzyl alcohol offers a significant clinical advantage over other alternatives in general use. It should be available as an alternative treatment option through the medical justification portion of the prior authorization process.

XI. Recommendations

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

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Thiazolidinediones
AHFS Class 682028
November 10, 2010

I. Overview

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-9] They are selective agonists of the peroxisome proliferator-activated receptor-gamma (PPARγ) receptor, which are found in tissues important for insulin action.[1-9] When activated, PPARγ regulates the transcription of insulin-responsive genes responsible for glucose production, transportation and utilization. PPARγ also plays a role in the regulation of fatty acid metabolism. The thiazolidinediones increase the insulin sensitivity of adipose tissue, skeletal muscle and the liver. This results in increased glucose uptake and metabolism, suppression of hepatic glucose production, and decreased plasma free fatty acid concentrations.[4-9]

Both pioglitazone and rosiglitazone are available in combination with either metformin or glimepiride. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[5.9] Glimepiride improves glycemic control by stimulating the release of insulin from pancreatic beta cells.[6,8]

The thiazolidinedione class was last reviewed in May 2010. The cardiovascular safety of rosiglitazone has been a controversial issue since 2007. In February 2010, the FDA notified healthcare professionals that it was reviewing the primary data from the RECORD trial to further assess the cardiovascular risks with rosiglitazone. They stated that there were no new conclusions or recommendations about the use of rosiglitazone in the treatment of type 2 diabetes. The FDA advised healthcare professionals to continue to follow the recommendations in the prescribing information when using rosiglitazone. However, on September 23, 2010, the FDA notified healthcare providers that the use of rosiglitazone is going to be significantly restricted in response to data that suggested an increased risk of cardiovascular events with the drug.[82] The FDA will be requiring the manufacturer to develop a risk evaluation and mitigation strategy (REMS). Under the REMS, rosiglitazone will only be available to new patients if they are unable to achieve glycemic control on other antidiabetic agents and are unable to take pioglitazone. Current users of rosiglitazone will be able to continue taking the drug if they are benefiting from it. The FDA also halted the TIDE trial, which was evaluating the cardiovascular effects of rosiglitazone and pioglitazone in patients with type 2 diabetes.[82,85]

The thiazolidinediones that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available; however, metformin and glimepiride are available generically in a separate formulation.

Table 1. Thiazolidinediones Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Pioglitazone	tablet	Actos®	Actos®
Pioglitazone and glimepiride	tablet	Duetact®	none
Pioglitazone and metformin	tablet	Actoplus Met®, Actoplus Met XR®	none
Rosiglitazone	tablet	Avandia®	Avandia®
Rosiglitazone and glimepiride	tablet	Avandaryl®	Avandaryl®
Rosiglitazone and metformin	tablet	Avandamet®	Avandamet®

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the thiazolidinediones are summarized in Table 2. For a comprehensive overview of the treatment of diabetes mellitus, please refer to the appendix.

Table 2. Treatment Guidelines Using the Thiazolidinediones

Clinical Guideline	Recommendation(s)
American Diabetes Association (ADA): **Standards of Medical Care in Diabetes[10] (2010)**	Treatment of Type 2 Diabetes • Refer to the ADA/EASD consensus statement on the management of individuals with type 2 diabetes for specific treatment recommendations.[11] Prevention/Delay of Type 2 Diabetes • Individuals with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) should receive counseling on lifestyle changes. • Metformin should be the only drug considered for use in diabetes prevention. Other antidiabetic agents are not recommended due to adverse events and lack of persistence of effect demonstrated in some studies.
American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD): **Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy[11] (2009)**	General Considerations • There is insufficient data to support recommending one class of agents or a combination of medications over other classes or combinations with regards to effects on complications. • The effects on long-term complications of diabetes are likely due to the level of glycemic control rather than the specific intervention. • Tier 1 interventions represent the best established and most effective therapeutic strategy for achieving glycemic goals. In selected clinical settings, the tier 2 algorithm may be considered. Tier 1 Interventions • Lifestyle intervention and metformin should be initiated as the first step in treating patients with type 2 diabetes mellitus. • If lifestyle intervention and metformin fail to achieve glycemic goals within 2-3 months, insulin or a sulfonylurea should be added. • If lifestyle, metformin, and either a sulfonylurea or basal insulin do not achieve glycemic goals, insulin therapy should be started or intensified. • The addition of a third oral agent can be considered, especially if the A1C is <8.0%; however, this is not preferred as it is no more effective in lowering glucose than initiating or intensifying insulin. Tier 2 Interventions • Lifestyle intervention and metformin should be initiated as the first step in treating patients with type 2 diabetes mellitus. • If lifestyle intervention and metformin fail to achieve glycemic goals within 2-3 months, the addition of exenatide or pioglitazone may be considered if hypoglycemia is a concern. Rosiglitazone is not recommended. • If the above interventions are not effective in achieving target A1C, addition of a sulfonylurea could be considered. • If further adjustments are needed, the above tier 2 interventions should be stopped and basal insulin should be added to metformin. Special Considerations • In severely uncontrolled diabetes, the treatment of choice is insulin therapy in combination with lifestyle intervention. • After improvement in symptoms, oral agents may be added and insulin therapy may be withdrawn (if appropriate).
American Association of Clinical Endocrinologists	Management of Patients With A1C Levels of 6.5% to 7.5% • Monotherapy:

Clinical Guideline	Recommendation(s)
(AACE)/American College of Endocrinology (ACE) Consensus Panel on Type 2 Diabetes Mellitus: **An Algorithm for Glycemic Control** [12] **(2009)**	○ Metformin, TZDs, DPP-4 inhibitors, and α-glucosidase inhibitors (AGIs) are all appropriate for use as monotherapy. These agents have a minimal risk of hypoglycemia. ○ Metformin is the cornerstone of monotherapy because of its safety and efficacy. ○ In patients with insulin resistance, metabolic syndrome, and/or nonalcoholic fatty liver disease, TZDs may be preferred. • Dual therapy: ○ Metformin is the cornerstone of dual therapy because of its safety and efficacy. ○ When metformin is contraindicated, a TZD may be used instead of metformin. These agents are considered insulin sensitizers. ○ The second component of the dual therapy regimen includes the agents in the following order: incretin mimetic, DPP-4 inhibitor, or an insulin secretagogue (glinide and sulfonylurea). ○ The combination of a TZD with metformin is recommended with a higher priority than a glinide or sulfonylurea because of a lower risk of hypoglycemia and greater flexibility in timing of administration. ○ 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. These combinations may result in gastrointestinal adverse events. • Triple therapy: ○ The following combinations are considered for triple therapy in the following order: 1. Metformin + GLP-1 agonist + TZD 2. Metformin + GLP-1 agonist + glinide 3. Metformin + GLP-1 agonist + sulfonylurea 4. Metformin + DPP-4 inhibitor + TZD 5. Metformin + DPP-4 inhibitor + glinide 6. Metformin + DPP-4 inhibitor + sulfonylurea ○ The third component of the triple therapy regimen includes a TZD, glinide, or sulfonylurea. They are recommended in the following order to minimize the risk of hypoglycemia: TZD, glinide, or sulfonylurea. • Insulin therapy: ○ Metformin is the most commonly used and safest medication to combine with insulin. ○ TZDs in combination with insulin have been associated with weight gain, fluid retention, congestive heart failure, and increased risk of fractures. Recent clinical trials (ADVANCE, VADT, and ACCORD) showed no increased risk of mortality associated with rosiglitazone. The PROACTIVE trial showed a small beneficial effect of pioglitazone on cardiac events. <u>Management of Patients With A1C Levels of 7.6% to 9.0%</u> • Dual therapy should be started initially if the patient has an A1C of 7.6% to 9.0% because no single agent is likely to achieve the A1C goal. • Dual therapy: ○ The following combinations are recommended for dual

Clinical Guideline	Recommendation(s)
	therapy in the following order: 1. Metformin + GLP-1 agonist 2. Metformin + DPP-4 inhibitor 3. Metformin + TZD 4. Metformin + sulfonylurea 5. Metformin + glinide o The lower position of TZDs is due to the risks of weight gain, fluid retention, congestive heart failure, and fractures. • Triple therapy: o The following combinations are recommended for triple therapy in the following order: 1. Metformin + GLP-1 agonist + TZD 2. Metformin + DPP-4 inhibitor + TZD 3. Metformin + GLP-1 agonist + sulfonylurea 4. Metformin + DPP-4 inhibitor + sulfonylurea 5. Metformin + TZD + sulfonylurea o TZDs are assigned a priority greater than that for a sulfonylurea because of their low risk of hypoglycemia. o The combination of metformin, TZD, and sulfonylurea is in the lowest recommended position due to the increased risk of weight gain and hypoglycemia. • Insulin therapy: o Insulin therapy for patients with an A1C of 7.6% to 9.0% follows the same principles as outlined previously for patients with an A1C level of 6.5% to 7.5%. <u>Management of Patients With A1C Levels of >9.0%</u> • If the A1C is >9.0%, then the probability of reaching an A1C ≤6.5% is low. If the patient is asymptomatic, initiating a triple therapy regimen may be appropriate. If the patient is symptomatic, or therapy with medications has failed, it is appropriate to initiate insulin therapy, either with or without additional oral agents. • Combination therapy: o The following 8 combinations are considered: 1. Metformin + GLP-1 agonist 2. Metformin + GLP-1 agonist + sulfonylurea 3. Metformin + DPP-4 inhibitor 4. Metformin + DPP-4 inhibitor + sulfonylurea 5. Metformin + TZD 6. Metformin + TZD + sulfonylurea 7. Metformin + GLP-1 + TZD 8. Metformin + DPP-4 inhibitor + TZD o A sulfonylurea or a TZD may be added. The sulfonylurea is preferred because of its greater efficacy and more rapid onset of action. o If the patient is symptomatic, or if the patient has already failed treatments similar to those listed above, then it is appropriate to initiate insulin therapy. • Insulin therapy: o Insulin therapy for patients with A1C levels exceeding 9.0% follows the same principles as outlined previously for patients with A1C values of ≤9.0%.
American Association of Clinical Endocrinologists (AACE): **Medical Guidelines for Clinical Practice for the Management of Diabetes**	• Refer to the updated AACE/ACE consensus statement on the management of individuals with type 2 diabetes for specific treatment recommendations.[12]

Clinical Guideline	Recommendation(s)
Mellitus[13] **(2007)**	

National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: Newer Agents[14]**
(2009)
	• Consider adding a thiazolidinedione (instead of a sulfonylurea) as second-line therapy to first-line metformin when control of blood glucose is inadequate (A1C ≥6.5%) if the person is at risk of hypoglycemia, does not tolerate a sulfonylurea, or a sulfonylurea is contraindicated.
	• Consider adding a thiazolidinedione as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose is inadequate (A1C ≥6.5%) if the person does not tolerate metformin or metformin is contraindicated.
	• Consider adding a thiazolidinedione as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose is inadequate (A1C ≥7.5%) and insulin is unacceptable or inappropriate.
	• Only continue thiazolidinedione therapy if the person has had a beneficial metabolic response (>0.5% reduction in A1C in 6 months).
	• Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to thiazolidinedione therapy or for a person who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.
	• A thiazolidinedione may be preferable to a DPP-4 inhibitor if:
	  o The person has marked insulin insensitivity OR
	  o A DPP-4 inhibitor is contraindicated OR
	  o The person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor
	• There may be some individuals for whom either a thiazolidinedione or a DPP-4 inhibitor may be suitable.

National Institute for Health and Clinical Excellence (NICE): **Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)[15]** **(2008)**	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes. • Refer to the updated NICE recommendations for specific treatment recommendations using the thiazolidinediones.[14]
Institute for Clinical Systems Improvement (ICSI): **Diagnosis and Management of Type 2 Diabetes Mellitus in Adults[16]** **(2009)**	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes due to the low risk of hypoglycemia, side effects, and lack of weight gain. • Sulfonylureas and thiazolidinediones are acceptable secondary choices if metformin is contraindicated. • Combination therapy may be required to achieve goals. • If treatment goals are not met on oral agents, or if oral agents are contraindicated, then it is necessary to begin insulin either alone or as an adjunct to oral therapy. • If renal function is a concern, thiazolidinediones may be considered, but the potential risks of fluid retention and increased risk of cardiac events need to be considered. • Thiazolidinediones must be used with caution in patients with Class I and II congestive heart failure or patients at high risk for congestive heart failure. Thiazolidinediones should not be used in Class III and IV congestive heart failure. • Rosiglitazone may increase cardiovascular events and is not recommended. When a thiazolidinedione is used, pioglitazone is preferred due to concerns about rosiglitazone cardiovascular safety in observational analysis.

Clinical Guideline	Recommendation(s)
International Diabetes Federation (IDF) Clinical Guidelines Task Force: Global Guideline for Type 2 Diabetes[17] (2005)	• Metformin is recommended as first-line therapy for the treatment of type 2 diabetes. • Sulfonylureas should be considered when metformin fails, or as first-line therapy in non-overweight patients. • When glucose concentrations are not controlled to target levels, thiazolidinediones may be added to metformin as an alternative to sulfonylureas, added to a sulfonylurea when metformin is contraindicated, or used in addition to metformin/sulfonylurea combination therapy.

III. Indications

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

Table 3. FDA-Approved Indications for the Thiazolidinediones[1-9]

Indication	Pioglitazone	Pioglitazone/ Glimepiride	Pioglitazone/ Metformin	Rosiglitazone	Rosiglitazone/ Glimepiride	Rosiglitazone/ Metformin
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔			✔ *		
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and a sulfonylurea or who have inadequate glycemic control on a thiazolidinedione alone or a sulfonylurea alone		✔				
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with a thiazolidinedione and metformin or who have inadequate glycemic control on a thiazolidinedione alone or metformin alone			✔			
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both rosiglitazone and glimepiride is appropriate					✔ *	
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both rosiglitazone and metformin is appropriate						✔ *

*The coadministration of rosiglitazone, rosiglitazone/glimepiride or rosiglitazone/metformin and insulin is not recommended. The use of rosiglitazone, rosiglitazone/glimepiride or rosiglitazone/metformin with nitrates is not recommended.

IV. Pharmacokinetics

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

Table 4. Pharmacokinetic Parameters of the Thiazolidinediones[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Pioglitazone	50	>99	Liver, extensive	Renal (15-30) Feces	3-7
Pioglitazone and glimepiride	P: 50 G: 100	>99	Liver, extensive	P: Renal (15-30) G: Renal (60) Feces (40)	8-11
Pioglitazone and metformin	P: 50 M: 50-60	P:>99 M: Negligible	Liver, extensive	P: Renal (15-30) M: Renal (90)	3-7
Rosiglitazone	99	99.8	Liver, extensive	Renal (64) Feces (23)	3-4
Rosiglitazone and glimepiride	R: 99 G: 100	R: 99.8 G: 99.5	Liver, extensive	R: Renal (64) Feces (23) G: Renal Feces (40)	3-7
Rosiglitazone and metformin	R: 99 M: 50-60	R: 99.8 M: Negligible	Liver, extensive	R: Renal (64) Feces (23) M: Renal (90)	1.5-6.2

G=glimepiride, M=metformin, P=pioglitazone, R=rosiglitazone

V. Drug Interactions

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

Table 5. Significant Drug Interactions with the Thiazolidinediones[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Metformin	1	Iodine-containing radiopaque agents	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin; therefore, there is an increased risk of metformin-induced lactic acidosis.
Sulfonylureas	1	Quinolones	The hypoglycemic effect of sulfonylureas may be increased by quinolones especially in elderly patients with renal compromise. Hypoglycemia symptoms including lightheadedness, diaphoresis, tachycardia and various neurologic and psychiatric disturbances may occur. The mechanism of this interaction is unknown.
Pioglitazone, rosiglitazone	2	Gemfibrozil	Gemfibrozil may inhibit the metabolism of thiazolidinediones and increase plasma concentrations. There is an increased risk of hypoglycemia and other adverse effects.

Generic Name(s)	Significance Level	Interaction	Mechanism
Pioglitazone, rosiglitazone	2	Rifamycins	Rifamycins may increase the metabolism of the thiazolidinediones, reducing their plasma concentrations and half-lives, resulting in decreased glycemic control.
Sulfonylureas	2	Azole antifungals	Azole antifungals may inhibit cytochrome P450 2C9-mediated metabolism of sulfonylureas. The hypoglycemic effects of sulfonylureas may be increased by azole antifungals.
Sulfonylureas	2	Chloramphenicol	Chloramphenicol may reduce hepatic clearance of certain sulfonylureas and cause an increased hypoglycemic response. Symptoms of hypoglycemia: lightheadedness, diaphoresis, tachycardia, and various neurologic and psychiatric disturbances may occur.
Sulfonylureas	2	Clofibrate	Clofibrate may cause an increased hypoglycemic response to certain sulfonylureas through an unknown mechanism.
Sulfonylureas	2	Diazoxide	Diazoxide may decrease endogenous insulin release and cause increases in glucose and free fatty acids resulting in a decrease in glycemic control in patients stabilized on a sulfonylurea.
Sulfonylureas	2	Fenfluramine and derivatives	The hypoglycemic effects of sulfonylureas may be increased by fenfluramine and derivatives. Pharmacologic effects may be additive.
Sulfonylureas	2	Monoamine oxidase inhibitors (MAOIs)	MAOIs may enhance the hypoglycemic action of sulfonylureas through an unknown mechanism. Monitor blood glucose concentrations and adjust the doses of the sulfonylurea accordingly.
Sulfonylureas	2	Phenylbutazone	The hypoglycemic effects of sulfonylureas may be increased. Symptoms of hypoglycemia: lightheadedness, diaphoresis, tachycardia, and various neurologic and psychiatric disturbances may occur.
Sulfonylureas	2	Rifamycins	Rifamycins may decrease the half-life and increase the clearance of sulfonylureas through increased metabolism.
Sulfonylureas	2	Sulfonamides	Sulfonamides may impair the metabolism of sulfonylureas and enhance the hypoglycemic effects of sulfonylureas.

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

VI. Adverse Drug Events

The most common adverse drug events reported with the thiazolidinediones are listed in Table 6. The boxed warnings for the thiazolidinediones are listed in Tables 7 – 12. In February 2010, the FDA notified healthcare professionals and consumers that they are reviewing the primary data from the RECORD trial to assess cardiovascular risks with rosiglitazone.[82] They are also continuing to monitor the results of observational studies that have been published. The FDA stated that there are no new conclusions or recommendations about the use of rosiglitazone in the treatment of type 2 diabetes. Once they complete their review of the data from the RECORD study, the FDA will present the totality of new and existing cardiovascular safety data on rosiglitazone at a public meeting in July 2010. FDA recommends that healthcare professionals follow the recommendations in the prescribing information when using rosiglitazone.[82]

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

Adverse Events	Pioglitazone	Pioglitazone/ Glimepiride	Pioglitazone/ Metformin	Rosiglitazone	Rosiglitazone/ Glimepiride	Rosiglitazone/ Metformin
Cardiovascular						
Angina	-	-	-	✔	✔	✔
Cardiac arrest	-	-	-	✔	✔	✔
Coronary artery disease	-	-	-	✔	✔	✔
Coronary thrombosis	-	-	-	✔	✔	✔
Edema	5-15	6-12	3-11	5-15	3	6
Heart failure	<6	<6	<6	2-3	<1	<1
Hypertension	-	-	-	4	2-3	4
Myocardial infarction	-	-	-	<1	<1	<1
Myocardial ischemia	-	-	-	3	3	3
Central Nervous System						
Asthenia	-	<2	-	-	<2	-
Dizziness	-	<2	5	-	<2	8
Fatigue	4	4	4	-	-	6
Headache	9	4-7	2-6	6	3-6	7-11
Dermatological						
Erythema	-	<1	-	-	<1	-
Maculopapular eruptions	-	<1	-	-	<1	-
Morbilliform eruptions	-	<1	-	-	<1	-
Pruritus	-	<1	-	<1	<1	<1
Rash	-	-	-	<1	<1	<1
Stevens-Johnson syndrome	-	-	-	<1	<1	<1
Urticaria	-	<1	-	<1	<1	<1
Endocrine and Metabolic						
Hypoglycemia	✔	13-16	✔	1-3	4-6	3
Lactic acidosis	-	-	✔	-	-	✔
Weight gain	✔	9-13	3-7	<1	<1	<1
Gastrointestinal						
Abdominal pain	-	-	-	-	-	5
Constipation	-	-	-	-	-	5
Diarrhea	-	4-6	5-6	3	3	13-14
Dyspepsia	-	-	-	-	-	10
Loose stools	-	-	-	-	-	5
Nausea	-	4-5	4-6	-	1	16
Tooth disorder	5	5	2-5	-	-	-
Vomiting	-	-	-	-	-	16
Genitourinary						
Urinary tract infection	-	6-7	5-6	-	-	-

Adverse Events	Pioglitazone	Pioglitazone/ Glimepiride	Pioglitazone/ Metformin	Rosiglitazone	Rosiglitazone/ Glimepiride	Rosiglitazone/ Metformin
Hematologic						
Anemia	≤2	≤2	≤2	2	2	4-7
Hematocrit decreased	✔	✔	✔	<1	<1	<1
Hemoglobin decreased	✔	✔	✔	<1	<1	<1
Hemolytic anemia	-	✔	-	-	✔	-
Leukopenia	-	-	-	<1	<1	<1
Thrombocytopenia	-	-	-	<1	<1	<1
Laboratory Test Abnormalities						
Bilirubin increased	-	-	-	<1	<1	<1
CPK increased	<1	<1	<1	-	-	-
Hepatic failure	<1	<1	<1	<1	<1	<1
Hepatitis	<1	<1	<1	<1	<1	<1
Jaundice	-	-	-	<1	<1	<1
Transaminases increased	<1	<1	<1	<1	<1	<1
Vitamin B12 decreased	-	-	7	-	-	7
Musculoskeletal						
Arthralgia	-	-	-	5	5	5
Back pain	-	-	-	4-5	4-5	5
Fractures	<1	<1	<1	<1	<1	<1
Limb pain	-	4-5	-	-	-	-
Myalgia	5	5	2-5	-	-	-
Respiratory						
Dyspnea	✔	<1	✔	<1	<1	<1
Nasopharyngitis	5	5	5	6	4-5	6
Pleural effusion	-	-	-	<1	<1	<1
Pulmonary edema	<1	<1	<1	<1	<1	<1
Sinusitis	6	6	4-5	3	3	6
Upper respiratory tract infection	13	12-15	12-16	4-10	4-10	9-16
Other						
Anaphylactic reaction	-	-	-	<1	<1	<1
Angioedema	-	-	-	<1	<1	<1
Bladder cancer	<1	<1	<1	-	-	-
Blurred vision	<1	<1	<1	<1	<1	<1
Flu-like syndrome	-	-	-	-	-	1
Macular edema	<1	<1	<1	<1	<1	<1
Viral infection	-	-	-	-	-	5
Visual acuity decreased	<1	<1	<1	<1	<1	

✔ Percent not specified
\- Event not reported

Table 7. Boxed Warning for Pioglitazone[1]

WARNING
Congestive heart failure (CHF): Thiazolidinediones, including pioglitazone, cause or exacerbate CHF in some patients. After initiation of pioglitazone, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, manage the heart failure according to the current standards of care. Furthermore, discontinuation or dose reduction of pioglitazone must be considered. Pioglitazone is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone in patients with established New York Heart Association (NYHA) class III or IV heart failure is contraindicated.

Table 8. Boxed Warning for Pioglitazone/Glimepiride[1]

WARNING
Congestive heart failure: Thiazolidinediones, including pioglitazone, which is a component of pioglitazone/glimepiride, cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of pioglitazone/glimepiride, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, manage the heart failure according to the current standards of care. Furthermore, consider discontinuation of pioglitazone/glimepiride. Pioglitazone/glimepiride is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone/glimepiride in patients with established New York Heart Association (NYHA) class III or IV heart failure is contraindicated.

Table 9. Boxed Warning for Pioglitazone/Metformin[1]

WARNING
Congestive heart failure: Thiazolidinediones, including pioglitazone, which is a component of pioglitazone/metformin, cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of pioglitazone/metformin, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, manage the heart failure according to the current standards of care. Furthermore, consider discontinuation or dose reduction of pioglitazone/metformin. Pioglitazone/metformin is not recommended in patients with symptomatic heart failure. Initiation of pioglitazone/metformin in patients with established New York Heart Association (NYHA) class III or IV heart failure is contraindicated. **Lactic acidosis:** Lactic acidosis is a rare but serious complication that can occur because of metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, pioglitazone/metformin should be discontinued and the patient hospitalized immediately.

Table 10. Boxed Warning for Rosiglitazone[1]

WARNING
Congestive heart failure and myocardial ischemia: Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of rosiglitazone and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain; dyspnea; and/or edema). If these signs and symptoms develop, manage the heart failure according to current standards of care. Furthermore, consider discontinuation or dose reduction of rosiglitazone. Rosiglitazone is not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone in patients with established New York Heart Association (NYHA) class III or IV heart failure is contraindicated. A meta-analysis of 42 clinical studies (mean duration, 6 months; 14,237 total patients), most of which compared rosiglitazone with placebo, showed rosiglitazone to be associated with an increased risk of myocardial ischemic events, such as angina or myocardial infarction (MI). Three other studies (mean duration, 41 months; 14,067 total patients) comparing rosiglitazone with some other approved oral antidiabetic agents or placebo have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

Table 11. Boxed Warning for Rosiglitazone/Glimepiride[1]

WARNING
Congestive heart failure and myocardial ischemia: Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of rosiglitazone/glimepiride, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone/glimepiride must be considered. Rosiglitazone/glimepiride is not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone/glimepiride in patients with established New York Heart Association (NYHA) class III or IV heart failure is contraindicated. A meta-analysis of 42 clinical studies (mean duration, 6 months; 14,237 total patients), most of which compared rosiglitazone with placebo, showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction (MI). Three other studies (mean duration, 41 months; 14,067 total patients), comparing rosiglitazone with some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

Table 12. Boxed Warning for Rosiglitazone/Metformin[1]

WARNING
Congestive heart failure and myocardial ischemia: Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure (CHF) in some patients. After initiation of rosiglitazone/metformin, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone/metformin must be considered. Rosiglitazone/metformin is not recommended in patients with symptomatic heart failure. Initiation of rosiglitazone/metformin in patients with established New York Heart Association (NYHA) class III or IV heart failure is contraindicated. A meta-analysis of 42 clinical studies (mean duration, 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration, 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. **Lactic acidosis:** Lactic acidosis is a rare but serious metabolic complication that can occur because of metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal function impairment, and acute CHF. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, discontinue rosiglitazone/metformin and hospitalize the patient immediately.

VII. Dosing and Administration

The usual dosing regimens for the thiazolidinediones are listed in Table 13.

Table 13. Usual Dosing Regimens for the Thiazolidinediones[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Pioglitazone	Monotherapy: 15-30 mg once daily; maximum: 45 mg per day Combination with insulin: 15-30 mg once daily; maximum: 45 mg per day. The current insulin dose can be continued upon initiation of pioglitazone therapy. In patients receiving pioglitazone and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Combination with metformin: 15-30 mg once daily; maximum: 45 mg per day. The current metformin dose can be continued upon initiation of pioglitazone therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with pioglitazone. Combination with sulfonylureas: 15-30 mg once daily; maximum: 45 mg per day. The current sulfonylurea dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.	Safety and efficacy in pediatric patients have not been established.	Tablet: 15 mg 30 mg 45 mg
Pioglitazone and glimepiride	Currently on glimepiride monotherapy: 30 mg-2 mg or 30 mg-4 mg once daily Currently on pioglitazone monotherapy: 30 mg-2 mg once daily Switching from combination therapy of pioglitazone plus glimepiride as separate tablets: 30 mg-2 mg or 30 mg-4 mg based on the dose of pioglitazone and glimepiride already being taken Currently on a different sulfonylurea monotherapy or switching from combination therapy of pioglitazone plus a different sulfonylurea: 30 mg-2 mg once daily	Safety and efficacy in pediatric patients have not been established.	Tablet: 30 mg-2 mg 30 mg-4 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Pioglitazone and metformin	Type 2 Diabetes Mellitus: Tablet (IR): 15 mg-500 mg or 15 mg-850 mg once or twice daily; maximum pioglitazone 45 mg and 2,550 mg metformin Tablet (ER): 15 mg-1,000 mg or 30 mg-1,000 mg once daily; maximum pioglitazone 45 mg and 2,000 mg metformin	Safety and efficacy in pediatric patients have not been established.	Tablet (IR): 15 mg-500 mg 15 mg-850 mg Tablet (ER): 15 mg-1,000 mg 30 mg-1,000 mg
Rosiglitazone	Monotherapy: 4 mg once daily or 2 mg twice daily; maximum: 8 mg per day Combination with metformin: 4 mg once daily or 2 mg twice daily; maximum: 8 mg per day. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with rosiglitazone. Combination with sulfonylurea: 4 mg once daily or 2 mg twice daily; maximum: 8 mg per day. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased. Combination with sulfonylurea plus metformin: 4 mg once daily or 2 mg twice daily; maximum: 8 mg per day. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.	Safety and efficacy in pediatric patients have not been established.	Tablet: 2 mg 4 mg 8 mg
Rosiglitazone and glimepiride	Initial therapy: 4 mg-1 mg once daily; maximum: 8 mg-4 mg Current treatment with a sulfonylurea or thiazolidinedione: 4 mg-1 mg or 4 mg-2 mg once daily; maximum: 8 mg-4 mg Switching from combination therapy of rosiglitazone plus glimepiride as separate tablets: The usual starting dose of rosiglitazone/glimepiride is the dose of rosiglitazone and glimepiride already being taken.	Safety and efficacy in pediatric patients have not been established.	Tablet: 4 mg-1 mg 4 mg-2 mg 4 mg-4 mg 8 mg-2 mg 8 mg-4 mg
Rosiglitazone and metformin	Initial therapy: 2 mg-500 mg once or twice daily; maximum: 8 mg-2,000 mg Currently on metformin monotherapy: 4 mg rosiglitazone (total daily dose) plus the dose of metformin already	Safety and efficacy in pediatric patients have not been established.	Tablet: 2 mg-500 mg 2 mg-1,000 mg 4 mg-500 mg 4 mg-1,000 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	being taken; maximum: 8 mg-2,000 mg Currently on rosiglitazone monotherapy: 1,000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken; maximum: 8 mg-2,000 mg Switching from combination therapy of rosiglitazone plus metformin as separate tablets: The usual starting dose of rosiglitazone/metformin is the dose of rosiglitazone and metformin already being taken		

ER=extended-release, IR=immediate-release

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the thiazolidinediones are summarized in Table 14.

Table 14. Comparative Clinical Trials with the Thiazolidinediones

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cardiovascular Outcomes Trials				
Dormandy et al.[44] (2005) Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	DB, MC, PC, RCT (PROactive Study) Patients 35-75 years of age with type 2 diabetes, A1C >6.5% despite treatment with diet or oral antidiabetic agents with or without insulin, and extensive macrovascular disease	N=5,238 34.5 months (average time of observation)	Primary: Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, ACS, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle Secondary: Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke; cardiovascular death; and time to individual components of the primary composite end point	Primary: At least 1 event in the primary composite end point occurred in 514 patients taking pioglitazone and 572 patients taking placebo (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Secondary: Fewer patients on pioglitazone reached the main secondary end point (composite of all-cause mortality, MI and stroke) compared to placebo (301 vs 358 patients; HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). Significantly more reports of heart failure were noted in patients treated with pioglitazone compared to placebo (281 vs 198 patients; P<0.0001). Deaths due to heart failure did not differ significantly between the two study groups (25 for pioglitazone vs 22 for placebo; P=0.634). A greater number of patients on pioglitazone reported edema without heart failure compared to those on placebo (562 vs 341).
Wilcox et al.[21] (2007)	DB, MC, PC, RCT (PROactive 04 Study)	N=5,238 34.5 months	Primary: Composite of all-cause mortality,	Primary: In patients with prior stroke (N=486 pioglitazone and N=498 placebo), there was a trend of benefit with pioglitazone compared to placebo for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	Comparison of patients with and without prior stroke enrolled in the PROactive Study[44]	(average time of observation)	nonfatal MI (including silent MI), nonfatal stroke, ACS, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle Secondary: Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke	primary end point of all-cause mortality, nonfatal MI, nonfatal stroke, ACS, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle (event rate 20.2% pioglitazone vs 25.3% placebo; HR, 0.78; 95% CI, 0.60 to 1.02; P=0.0670). Secondary: In patients with prior stroke, there was a trend of benefit with pioglitazone compared to placebo for the main secondary end point of all-cause mortality, nonfatal MI or nonfatal stroke (event rate 15.6% pioglitazone vs 19.7% placebo; HR, 0.78; 95% CI, 0.58 to 1.06; P=0.1095). In patients with prior stroke, pioglitazone reduced fatal or nonfatal stroke (event rate 5.6% pioglitazone vs 10.2% placebo; HR, 0.53; 95% CI, 0.34 to 0.85; P=0.0085) and the composite of cardiovascular death, nonfatal MI or nonfatal stroke (event rate 13.0% pioglitazone vs 17.7% placebo; HR, 0.72; 95% CI, 0.52 to 1.00; P=0.0467). Higher event rates were observed in patients with prior stroke compared with those without prior stroke. In patients without prior stroke, no treatment effect was observed for a first stroke. In a subgroup analysis from PROactive, pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with type 2 diabetes.
Erdmann et al.[22] (2007) Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo	DB, MC, PC, RCT (PROactive 05 Study) Patients who qualified for entry into the PROactive study[44] on the basis of a previous MI 6 months or more before randomization	N=2,445 34.5 months (average time of observation)	Primary: Fatal or nonfatal MI (excluding silent MI); cardiovascular death or nonfatal MI; cardiovascular death, nonfatal MI or stroke; see PROactive Study Secondary: ACS; composite of nonfatal MI	Primary: Pioglitazone significantly reduced the risk of fatal and nonfatal MI (RR, 28%; P=0.045). There were no significant differences in the end point of cardiovascular death or nonfatal MI (P=0.201) or the end point of cardiovascular death, nonfatal MI or stroke (P=0.149). Secondary: Pioglitazone significantly reduced the risk of ACS (RR, 37%; P=0.035). Pioglitazone significantly reduced the risk of the cardiac composite end point of nonfatal MI, coronary revascularization, ACS and cardiac death (RR, 19%; P=0.033).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.			(excluding silent MI), coronary revascularization, ACS, or cardiac death; see PROactive Study	PROactive: The differences in the primary and main secondary end points defined in the main PROactive study did not reach significance in the MI population (P=0.135 and P=0.0585, respectively); however, there was a consistently lower number of events in the pioglitazone-treated patients for all of the end points. The rate of heart failure and heart failure requiring hospitalization (in patients with a previous MI) were significantly higher in the pioglitazone group compared to placebo (13.5% vs 9.6%; P=0.003 and 7.5% vs 5.2%; P=0.022, respectively). The rates of fatal heart failure were similar (1.4% with pioglitazone vs 0.9% with placebo; P=0.283).
Erdmann et al.[23] (2007) Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	DB, MC, PC, RCT (PROactive 08 Study) Patients enrolled into the PROactive study[44] who developed serious heart failure defined as heart failure that required hospitalization or prolonged a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity	N=5,238 34.5 months (average time of observation)	Primary: Composite of all-cause mortality, nonfatal MI (including silent MI), nonfatal stroke, ACS, endovascular or surgical intervention on coronary or leg arteries, or amputation above the ankle Secondary: Composite of all-cause mortality, nonfatal MI (excluding silent MI) and nonfatal stroke	Primary: Among patients with a serious heart failure event, subsequent all-cause mortality was proportionately lower with pioglitazone (40 of 149 [26.8%] vs 37 of 108 [34.3%] with placebo; P=0.1338). Proportionately fewer pioglitazone patients with serious heart failure went on to have an event in the primary end point (47.7% with pioglitazone vs 57.4% with placebo; P=0.0593). Secondary: More pioglitazone (5.7%) than placebo patients (4.1%) had a serious heart failure event during the study (P=0.007). However, mortality due to heart failure was similar (25 of 2,605 [0.96%] for pioglitazone vs 22 of 2,633 [0.84%] for placebo; P=0.639). Significantly fewer pioglitazone patients with serious heart failure went on to have an event in the main secondary end point (34.9% with pioglitazone vs 47.2% with placebo; P=0.025).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wilcox et al.[73] (2008) Pioglitazone 15 mg (month 1) QD titrated to 30 mg QD (month 2) and to 45 mg QD (month 3) if tolerated vs placebo Study drugs were taken in addition to the patients' glucose-lowering drugs and other medications.	DB, MC, PC, RCT (PROactive 10 Study) Patients 35-75 years of age with type 2 diabetes, A1C >6.5% despite treatment with diet or oral antidiabetic agents with or without insulin, and extensive macrovascular disease	N=5,238 34.5 months (average time of observation)	Primary: Analysis of the prespecified main secondary end point (MACE) and additional MACE end points (MACE1 through MACE 7)	Primary: Pioglitazone was associated with a 16% reduction in the main secondary end point of MACE compared to placebo (P=0.027). In the pioglitazone group, 9.9% of patients experienced an event from the MACE1 composite end point compared to 11.9% of patients receiving placebo (HR 0.82; 95% CI, 0.70 to 0.97; P=0.0201). Fewer patients receiving pioglitazone experienced an event from the MACE2 end point compared to placebo (HR 0.83; 95% CI, 0.72 to 0.96; P=0.0103). A similar result was observed for other end points, including MACE3 (P=0.0051), MACE4 (P=0.0120), MACE5 (P=0.0132), and MACE6 (P=0.0034). There was no significant difference in the MACE7 end point. MACE = all-cause mortality, nonfatal MI, nonfatal stroke MACE1 = cardiovascular mortality, nonfatal MI, or nonfatal stroke MACE2 = all-cause mortality, nonfatal MI, nonfatal stroke, ACS MACE3 = cardiovascular mortality, nonfatal MI, nonfatal stroke, ACE MACE4 = cardiac mortality, nonfatal MI, nonfatal stroke MACE5 = cardiac mortality, nonfatal MI, ACS MACE6 = cardiac mortality, nonfatal MI, nonfatal stroke, ACS MACE7 = cardiac mortality, nonfatal MI
Home et al.[27] (2007) Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	RCT, MC, OL, (RECORD interim analysis) Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (A1C 7% to	N=4,447 Mean follow-up 3.75 years	Primary: Hospitalization or death from cardiovascular causes Secondary: Death from cardiovascular causes and from any cause, MI, CHF, and composite of death from	Primary: For adjudicated primary end points (hospitalization or death from cardiovascular causes), the hazard ratio was 1.08 (95% CI, 0.89 to 1.31; P=0.43) with 217 events in the rosiglitazone group and 202 events in the control group. An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication. Secondary: There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: death from cardiovascular causes (HR, 0.83; 95% CI, 0.51 to 1.36; P=0.46) or any cause (HR, 0.93; 95% CI, 0.67 to 1.27; P=0.63), MI (HR, 1.16; 95% CI, 0.75 to 1.81; P=0.50), or the composite of cardiovascular death, MI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	9%)		cardiovascular causes, MI and stroke	and stroke (HR, 0.97; 95% CI, 0.73 to 1.29; P=0.83). However, the power to detect significant differences was low, as reflected by the wide 95% CI. Patients in the rosiglitazone group had a significantly higher risk of CHF than did patients in the control group, with 38 vs 17 adjudicated events (HR, 2.24; 95% CI, 1.27 to 3.97; P=0.006).
Home et al.[69] (2009) Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	RCT, MC, OL, (RECORD) Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and inadequate glycemic control (A1C 7% to 9%)	N=4,458 Mean follow-up 5.5 years	Primary: Time to first cardiovascular hospitalization or cardiovascular death Secondary: Cardiovascular death, all-cause mortality, myocardial infarction, stroke, composite of cardiovascular death, myocardial infarction, and stroke	Primary: The primary end point (cardiovascular hospitalization or cardiovascular death) occurred in 321 and 323 participants assigned to the rosiglitazone and active control groups, respectively (HR 0.99; 95% CI, 0.85–1.16; P=0.93). Secondary: There was no statistically significant difference between rosiglitazone and active controls for the following end points: cardiovascular death (HR 0.84; 95%, CI 0.59 to 1.18; P=0.32), all-cause mortality (HR 0.86; 95% CI, 0.68 to 1.08; P=0.19), myocardial infarction (HR 1.14; 95% CI, 0.80 to 1.63; P=0.47), stroke (HR 0.72; 95% CI, 0.49 to 1.06; P=0.10), and the composite of CV death, MI or stroke (HR 0.93; 95% CI, 0.74 to 1.15; P=0.50). Heart failure occurred in 61 patients receiving rosiglitazone compared to 29 patients receiving active control (HR 2.10; 95% CI, 1.35 to 3.27; P=0.0010). There were no serious adverse-event reports of macular edema. The incidence of bone fractures was higher in the rosiglitazone group than in the active control group (RR 1.57; 95% CI, 1.26 to 1.97; P<0.0001). The risk was higher in women than in men (RR 1.82; 95% CI, 1.37 to 2.41 vs RR 1.23; 95% CI, 0.85 to 1.77; P=0.10). The excess of fractures in patients on rosiglitazone was primarily in the upper limb (RR 1.57; 95% CI, 1.12 to 2.19; P=0.0095) and distal lower limb (RR 2.60; 95% CI, 1.67 to 4.04; P<0.0001). Hip and femur fracture did not increase with rosiglitazone treatment. There was a nonsignificant increase in spinal fractures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Lincoff et al.[45] (2007) Pioglitazone monotherapy vs metformin, placebo, sulfonylureas or rosiglitazone or pioglitazone combination therapy with insulin, metformin, or sulfonylureas vs active comparator or placebo	MA Adult patients with type 2 diabetes mellitus and inadequate glycemic control	N=16,390 (19 trials) 4 months to 3.5 years	Primary: Composite of death from any cause, MI or stroke Secondary: Incidence of serious heart failure	Primary: Death, MI or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72 to 0.94; P=0.005). Individual components of the primary end point were reduced with pioglitazone treatment with varying degrees of statistical significance (death HR, 0.92; P=0.38, MI HR, 0.81; P=0.08, death and MI HR, 0.85; P=0.04, and stroke HR, 0.80; P=0.09). Progressive separation of time-to-event curves became apparent after approximately 1 year of therapy. Secondary: Serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control patients (HR, 1.41; 95% CI, 1.14 to 1.76; P=0.002). The composite of serious heart failure and death was not significantly increased among patients receiving pioglitazone (HR, 1.11; 95% CI, 0.96 to 1.29; P=0.17).
Richter et al.[24] (2006) Pioglitazone monotherapy vs acarbose, metformin, placebo, repaglinide,	MA Adults with type 2 diabetes mellitus	N=6,200 (22 trials) 24 weeks to 34.5 months	Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects Secondary: Health-related quality of life, A1C	Primary: Only one trial (PROactive Study) evaluated mortality and morbidity as an end point. The primary composite end point (time from randomization to all-cause mortality, nonfatal MI, stroke, ACS, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group (HR, 0.90; 95% CI, 0.80 to 1.02; P=0.095). Time to the first event of the composite end point of death from any cause, MI and stroke indicated a statistically significant difference between pioglitazone and placebo (HR, 0.84; 95% CI, 0.72 to 0.98; P=0.027). The

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone, sulfonylurea or pioglitazone combination therapy vs combination therapy not containing pioglitazone				individual components of the primary composite end point did not disclose statistically significant differences between intervention and control groups. Significantly more patients developed heart failure requiring hospitalization following administration of pioglitazone (6% vs 4% on placebo; P=0.007). The percentage of overall and serious adverse events was comparable between intervention and control groups. Six trials reported a more pronounced (sometimes dose-related) decrease of hemoglobin after pioglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 0.75 g/dL. Fifteen trials evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment; 7 trials described a rise in body mass index up to 1.5 kg/m^2. Eleven of the 22 included trials showed data on hypoglycemic episodes: compared to the active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycemia. The relative risk for development of edema with pioglitazone compared to the control was 2.86 (95% CI, 2.14 to 3.18; P<0.00001) when results from 18 trials were pooled. Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide, gliclazide or glimepiride resulted in similar reductions of A1C compared to pioglitazone treatment.
Mannucci et al.[76] (2008) Pioglitazone vs active comparators, placebo, no treatment	MA Patients treated with pioglitazone (with or without type 2 diabetes)	N=21,180 (94 trials) Variable duration	Primary: All-cause mortality, non-fatal coronary event (defined as myocardial infarction, unstable angina or coronary revascularization), non-fatal chronic	Primary: <u>All-cause mortality</u>: In PROactive, pioglitazone treatment was not associated with a significant reduction in all-cause mortality. In non-diabetic subjects, only one death was observed occurring among pioglitazone-treated patients. In type 2 diabetic patients (excluding PROactive), the total number of deaths reported was 17 and 39 in the pioglitazone and comparator groups, respectively (RR 0.41; 95% CI, 0.23 to 0.72).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			heart failure (CHF) requiring hospitalization	When analyzing all trials, no significant reduction of mortality was observed with pioglitazone. Comparing different agents, pioglitazone was associated with a lower mortality rate than sulfonylureas. There was no significant difference in all-cause mortality with metformin, rosiglitazone, glitazars or placebo. When trials with zero events were included in the analysis, no significant difference was observed with sulfonylureas (RR 0.22; 95% CI, 0.05 to 1.03), metformin (RR 0.66; 95% CI 0.19 to 2.34), rosiglitazone (RR 0.49; 95% CI, 0.04 to 5.36), glitazars (RR 0.42; 95% CI, 0.11 to 1.61), or placebo (RR 0.16; 95% CI, 0.02 to 1.45). <u>Non-fatal coronary events:</u> In PROactive, pioglitazone significantly reduced the incidence of non-fatal coronary events. In non-diabetic subjects, only two non-fatal coronary events occurred and one case of heart failure in pioglitazone group were reported. In type 2 diabetes, 44 and 50 non-fatal coronary events were observed in pioglitazone and comparator groups, respectively (RR 0.82; 95% CI, 0.55 to 1.23). Combining trials with at least one event, the difference between pioglitazone and comparators was not statistically significant. <u>Non-fatal heart failure</u> In PROactive, pioglitazone was associated with an increased risk for CHF. In the other 40 trials reporting data on non-fatal heart failure requiring hospitalization, 58 cases were reported in pioglitazone-treated subjects and 39 in controls (RR 1.32; 95% CI, 0.88 to 1.98). Combining the results of all trials with at least one event except PROactive, the overall difference between pioglitazone and comparators was not statistically significant. When adding PROactive or excluding trials vs. dual PPARα/γ agonists pioglitazone was associated with a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				significant increase of risk for CHF. In comparison with different agents, pioglitazone was associated with an increased risk of CHF in placebo-controlled trials, while differences with sulfonylureas or glitazars did not reach statistical significance.
Nagajothi et al.[78] (2008) Pioglitazone vs active comparators (metformin and/or sulfonylurea) or placebo	MA Patients treated with pioglitazone	5 trials Variable duration	Primary: Myocardial infarction (MI) Secondary: Stroke, revascularization, total mortality, and cardiovascular mortality	Primary: The relative risk for MI was 0.86 (95% CI, 0.69 to 1.07; P=0.17). Secondary: The relative risk for stroke was 0.79 (95% CI, 0.61 to 1.02; P=0.07). The relative risk for total mortality was 0.94 (95% CI, 0.78 to 1.15; P=0.56). The relative risk for coronary revascularization was 0.40 (95% CI, 0.13 to 1.23; P=0.11. The relative risk for cardiovascular mortality was 0.92 (95% CI, 0.73 to 1.16; P=0.47).
Nissen et al.[26] (2007) Rosiglitazone monotherapy or combination therapy vs monotherapy or combination therapy with gliclazide*, glimepiride, glipizide, glyburide, insulin,	MA Patients with prediabetes or type 2 diabetes receiving rosiglitazone	27,843 (42 trials) 24 to 208 weeks	Primary: MI, death from cardiovascular causes	Primary: Rosiglitazone was associated with a significant increase in the risk of myocardial infarction compared to the control agent (OR, 1.43; 95% CI, 1.03 to 1.98; P=0.03). Compared to the control agent, rosiglitazone was associated with a trend toward increased cardiovascular death (OR, 1.64; 95% CI, 0.98 to 2.74; P=0.06). Although not a prespecified end point, the odds ratio for death from any cause with rosiglitazone was 1.18 (95% CI, 0.89 to 1.55; P=0.24).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin, placebo				
Singh et al.[28] (2007) Rosiglitazone vs placebo or other non-thiazolidinedione oral hypoglycemic agent (including glyburide or metformin)	MA Patients with prediabetes or type 2 diabetes receiving rosiglitazone	N=14,291 (4 trials) 1-4 years	Primary: Relative risks of MI, heart failure, and cardiovascular mortality	Primary: Rosiglitazone significantly increased the risk of myocardial infarction (94 vs 83; RR, 1.42; 95% CI, 1.06 to 1.91; P=0.02) and heart failure (102 vs 62; RR, 2.09; 95% CI, 1.52 to 2.88; P<0.001) compared to the control drug. There was no significant difference in the risk of cardiovascular mortality between the rosiglitazone and control group (59 vs 72; RR, 0.90; 95% CI, 0.63 to 1.26; P=0.53). Rosiglitazone had no effect on all-cause mortality (146 vs 180; RR, 0.99; 95% CI, 0.80 to 1.23; P=0.92).
Richter et al.[29] (2007) Rosiglitazone monotherapy vs glyburide, metformin, pioglitazone, placebo, repaglinide or rosiglitazone combination therapy vs	MA Patients with type 2 diabetes mellitus	N=3,888 (18 trials) 24 weeks to 4 years	Primary: Patient-oriented outcomes including mortality, morbidity, adverse effects Secondary: Health-related quality of life, metabolic control (A1C)	Primary: No study included mortality as a primary or secondary end point. While not an initial primary or secondary study end point, the ADOPT trial reported that the all-cause mortality was 2.3% in the rosiglitazone group, 2.1% in the metformin group and 2.2% in the glyburide group. The ADOPT trial also reported comparable hospitalization rates for any cause between rosiglitazone (11.6%), metformin (11.8%), and glyburide (10.4%) groups. Cardiovascular disease was increased in the rosiglitazone group compared to the glyburide group but not the metformin group with serious/total events reported in 3.4%/4.3% and 1.8%/2.8% of patients receiving rosiglitazone and glyburide, respectively (events were 3.2%/4.0% with metformin). Congestive heart failure was observed more frequently in patients receiving rosiglitazone (1.5%) than glyburide (0.6%) but not metformin (1.3%). The percentage of overall adverse events was comparable between the intervention and control groups (which included placebo arms); serious adverse events appeared to happen more often after rosiglitazone treatment (median of 6% versus 4% in the control groups). Median discontinuation rate following rosiglitazone administration was also higher than after

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination therapy not containing rosiglitazone				control therapy (median of 7% versus 4%). Three studies reported a more pronounced (apparently dose-related) decrease of hemoglobin after rosiglitazone intake in comparison to other active compounds or placebo; hemoglobin reductions ranged between 0.5 and 1.0 g/dL. Eleven studies evaluated body weight and observed an increase up to 5.0 kg after rosiglitazone treatment; 4 studies described a rise in body mass index up to 1.5 kg/m^2. Seven of the 18 included studies showed data on hypoglycemic episodes: compared to active monotherapy control, rosiglitazone treatment resulted in somewhat lower rates of hypoglycemia, especially when compared to sulfonylureas. Occurrence of edema was significantly raised when results of 9 studies were pooled (OR, 2.27; 95% CI, 1.83 to 2.81; P<0.00001). The ADOPT trial reported a higher incidence of fractures in women receiving rosiglitazone (9.30%) than metformin (5.08%; P<0.01) or glyburide (3.47%; P<0.01). Secondary: No study investigated health-related quality of life. Active glucose-lowering compounds like metformin, glibenclamide or glimepiride resulted in similar reductions of A1C compared to rosiglitazone treatment.
Lago et al.[32] (2007) Pioglitazone 15 to 45 mg per day or rosiglitazone 4 to 8 mg per day vs placebo, glibenclamide‡, glimepiride, metformin, metformin plus sulfonylurea	MA Patients with prediabetes or type 2 diabetes	N=20,191 (7 trials) 12 to 48 months	Primary: Development of CHF, risk of cardiovascular death	Primary: Three hundred and sixty of 20,191 patients who had either prediabetes or type 2 diabetes had CHF events (214 with thiazolidinediones and 146 with comparators). The overall event rate for CHF was 2.3% for patients receiving thiazolidinediones and 1.4% in the comparator group. Patients given pioglitazone (RR, 1.32; 95% CI, 1.04 to 1.68; P=0.02) or rosiglitazone (RR, 2.18; 95% CI, 1.44 to 3.32; P=0.0003) had increased risk for development of CHF across a wide background of cardiac risk compared to the control agent (combined RR, 1.72; 95% CI, 1.21 to 2.42; P=0.002). The risk for CHF did not differ for rosiglitazone and pioglitazone (RR, 1.74; 95% CI, 0.97 to 3.14; P=0.07). The overall event rate for cardiovascular death was 0.7% in both groups. The risk of cardiovascular death was not increased with pioglitazone (RR, 1.01; 95% CI, 0.51 to 2.01; P=0.98), rosiglitazone (RR, 0.91; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.63 to 1.32; P=0.63) or both thiazolidinediones (combined RR, 0.93; 95% CI, 0.67 to 1.29; P=0.68). The risk of cardiovascular death did not differ between both drug groups (RR, 1.01; 95% CI, 0.73 to 1.40; P=0.96).
Karter et al.[25] (2005) Patients initiated pioglitazone (15.2%), sulfonylureas (25.3%), metformin (50.9%), and insulin (8.6%) alone, or in addition to pre-existing therapies	OS Patients enrolled in the Kaiser Permanente Medical Care Program with type 2 diabetes who initiated any new diabetes treatment between October 1999 and November 2001	N=23,440 10.2 months (mean)	Primary: Time-to-incident admission to hospital for congestive heart failure (CHF)	Primary: Three hundred and twenty admissions for CHF were observed during the follow-up (mean 10.2 months) after drug initiation. Relative to patients initiating sulfonylureas, there were no significant increases in the incidence of hospitalization for CHF in those initiating pioglitazone (HR, 1.28; 95% CI, 0.85 to 1.92). There was a significantly higher incidence among those initiating insulin (HR, 1.56; 95% CI, 1.00 to 2.45) and lower incidence among those initiating metformin (HR, 0.70; 95% CI, 0.49 to 0.99).
Gerrits et al.[30] (2007) Pioglitazone vs rosiglitazone	OS Patients with type 2 diabetes who initiated treatment with pioglitazone or rosiglitazone between 2003 and 2006	N=29,911 1.2 to 1.3 years	Primary: Risk of hospitalization for acute MI Secondary: Risk of composite of acute MI or coronary revascularization	Primary: Among the patients that initiated pioglitazone, 1.1% was hospitalized for acute MI during follow-up compared to 1.4% for rosiglitazone. The unadjusted HR for hospitalization for acute MI associated with pioglitazone relative to rosiglitazone was 0.82 (95% CI, 0.67 to 1.01). After readjustment for baseline covariates (e.g., medical conditions, procedures and dispensed drugs), the HR was 0.78 (95% CI, 0.63 to 0.96). Secondary: There were 2.6% and 3.1% of patients in the pioglitazone and rosiglitazone groups, respectively, with a first event in the composite end point of acute MI or coronary revascularization. The adjusted HR for the composite of acute MI or coronary revascularization was 0.85 (95% CI, 0.75 to 0.98).
Graham et al.[87] (2010) Pioglitazone vs	OS Medicare beneficiaries ≥65 years of age with type 2 diabetes who	N=227,571 Median 105 days	Primary: Individual end points of acute myocardial infarction (AMI), stroke, heart	Primary: A total of 8,667 end points were observed during the study period. There were 1,746 AMIs (21.7% fatal), 1,052 strokes (7.3% fatal), 3,307 hospitalizations for heart failure (2.6% fatal), and 2,562 deaths from all causes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rosiglitazone	initiated treatment with pioglitazone or rosiglitazone through a Medicare Part D prescription drug plan from July 2006 to June 2009		failure, and all-cause mortality (death), and composite end point of AMI, stroke, heart failure, or death	For AMI, the adjusted hazard ratio was 1.06 for rosiglitazone compared to pioglitazone (95% CI, 0.96-1.18). For stroke, the adjusted hazard ratio was 1.27 for rosiglitazone compared to pioglitazone (95% CI, 1.12-1.45). For heart failure, the adjusted hazard ratio was 1.25 or rosiglitazone compared to pioglitazone (95% CI, 1.16-1.34). For all-cause mortality, the adjusted hazard ratio was 1.14 or rosiglitazone compared to pioglitazone (95% CI, 1.05-1.24). For the composite of AMI, stroke, heart failure, or death, the adjusted hazard ratio was 1.18 or rosiglitazone compared to pioglitazone (95% CI, 1.12-1.23). The attributable risk was 1.68 (95% CI, 1.27-2.08) excess events per 100 person-years of treatment with rosiglitazone compared with pioglitazone. The number needed to harm was 60 (95% CI, 48-79) treated for 1 year.
Lipscombe et al.[31] (2007) Pioglitazone or rosiglitazone vs other oral hypoglycemic agents	OS Patients with type 2 diabetes ≥66 years of age treated with at least 1 oral hypoglycemic agent between 2002 and 2005 with follow-up until March 2006	N=159,026 Median follow-up 3.8 years	Primary: Emergency department visit or hospitalization for CHF Secondary: Emergency department visit or hospitalization for acute MI, all-cause mortality	Primary: Current treatment with thiazolidinedione monotherapy was associated with a significantly increased risk of CHF (78 cases; adjusted RR, 1.60; 95% CI, 1.21 to 2.10; P<0.001) compared with other oral hypoglycemic agent combination therapies (3,478 CHF cases). The increased risk of CHF associated with thiazolidinedione use appeared limited to rosiglitazone. Secondary: Current treatment with thiazolidinedione monotherapy was associated with a significantly increased risk of acute MI (65 vs 3,695 cases; RR, 1.40; 95% CI, 1.05 to 1.86; P=0.02) and death (102 vs 5,529 cases; RR, 1.29; 95% CI, 1.02 to 1.62; P=0.03) compared with other oral hypoglycemic agent combination therapies. The increased risk of acute MI and death associated with thiazolidinedione use appeared limited to rosiglitazone.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Type 2 Diabetes – Monotherapy				
Khan et al.[33] (2002) Pioglitazone 15 mg to 45 mg QD vs rosiglitazone 2 mg to 4 mg QD or 4 mg BID	OL, PRO, RCT Patients previously stabilized on troglitazone with stable liver function (baseline A1C 7.9% for pioglitazone and 8.0% for rosiglitazone)	N=186 4 months	Primary: Effect on weight, A1C, lipoproteins	Primary: Both groups experienced equal and significant weight gain of 2.0 kg from baseline (P<0.01). No significant change in A1C from baseline or difference between groups was observed after 4 months. Pioglitazone had significant reductions in total cholesterol (–20 mg/dL) compared to rosiglitazone (5 mg/dL; P<0.01). Pioglitazone had significant reductions in LDL cholesterol (–16 mg/dL) compared to rosiglitazone (2 mg/dL; P<0.01).
Goldberg et al.[34] (2005) Pioglitazone 30 mg QD, titrated to 45 mg QD after 12 weeks vs rosiglitazone 4 mg QD, titrated to 4 mg BID after 12 weeks	DB, MC, PG, PRO, RCT Patients >35 years of age with type 2 diabetes with A1C >7%, TG ≥150 mg/dL, LDL cholesterol ≤130 mg/dL and C-peptide ≥1 ng/mL (baseline A1C was 7.6% for pioglitazone and 7.5% for rosiglitazone)	N =802 24 weeks	Primary: Effect on TG and lipoproteins, A1C	Primary: TG levels significantly decreased (–51.9 mg/dL) with pioglitazone while TG levels increased with rosiglitazone (13.1 mg/dL; P<0.001). Pioglitazone significantly increased HDL cholesterol (5.2 mg/dL) compared to rosiglitazone (2.4 mg/dL; P<0.001). Non-HDL cholesterol was significantly higher with rosiglitazone (25.7 mg/dL) compared to pioglitazone (3.6 mg/dL; P<0.001). Both treatment groups increased LDL cholesterol: however, smaller increases were observed with pioglitazone (12.3 mg/dL vs 21.3 mg/dL; P<0.001). LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone (P<0.001). LDL particle size increased more with pioglitazone (P=0.005). Similar reductions in A1C were observed with pioglitazone (–0.7%) and rosiglitazone (–0.6%; P=0.129). No difference between agents was observed in adverse events including edema, heart failure, liver function tests, blood pressure, and hypoglycemic episodes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Similar weight gain was observed with pioglitazone (2.0 kg) and rosiglitazone (1.6 kg; P=0.164).
Tran et al.[35] (2006) Pioglitazone 45 mg daily vs rosiglitazone 8 mg daily	RETRO Patients with type 2 diabetes who received a thiazolidinedione for >4 months after inadequate glycemic control on maximally tolerated doses of metformin and a sulfonylurea (baseline A1C was 9.5% for pioglitazone and 9.3% for rosiglitazone)	N=104 1 year	Primary: Proportion of patients with A1C ≤7.5% at 4 months and then at 12 months	Primary: After 4 months, 62% of patients on pioglitazone and 65% of the patients on rosiglitazone achieved an A1C ≤7.5%. Mean A1C levels were 7.4% for pioglitazone and 7.5% for rosiglitazone. Of the original population with an A1C of ≤7.5% at 4 months, 63% of patients on pioglitazone and 61% on rosiglitazone maintained an A1C ≤7.5% after 1 year.
Derosa et al.[36] (2004) Pioglitazone 15 mg once daily vs rosiglitazone 4 mg once daily	DB, MC, PG, RCT Patients ≥18 years with type 2 diabetes mellitus and metabolic syndrome, poor glycemic control (A1C >7.5%) or experienced adverse effects with diet and oral hypoglycemic agents, such as sulfonylureas or metformin, administered up to maximum tolerated	N=87 12 months	Primary: Changes in BMI, A1C, FPG, PPG, FPI, PPI, HOMA index, lipid profile, lipoprotein variables	Primary: Patients in the pioglitazone and rosiglitazone experienced a significant increase in mean BMI at 12 months compared with baseline (4.92% and 6.17%, respectively; both P<0.05). At 12 months, there was a 1.3% improvement from baseline in mean values for A1C (P<0.01), 19.3% in FPG (P<0.01), 16.3% in PPG (P<0.01), 42.4% in FPI (P<0.05), and 23.3% in PPI (P<0.05); no significant differences were found between treatment groups. Significant improvements in mean HOMA index were also observed in both groups compared to baseline (both P<0.01). Patients receiving pioglitazone experienced a significant improvement at 12 months in almost all variables of lipid metabolism from baseline including TC (–11%), LDL cholesterol (–12%), HDL cholesterol (15%), and apolipoprotein B (–10.6% [all P<0.05]). Patients receiving rosiglitazone experienced a significant increase in TC (14.9%), LDL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	dose			cholesterol (16.5%), TG (17.9%), and apolipoprotein B (10.3%; P<0.05). Of the 87 patients who completed the study, 3/45 of patients in the pioglitazone group and 5/42 patients in the rosiglitazone group had transient, mild-to-moderate adverse events that did not cause withdrawal from the trial.
Derosa et al.[37] (2006) Pioglitazone 15 mg once daily vs rosiglitazone 4 mg once daily	DB, MC, PG, RCT Patients ≥18 years with type 2 diabetes mellitus and metabolic syndrome, poor glycemic control (A1C >7.5%) or experienced adverse effects with diet and metformin, administered up to maximum tolerated dose	N=96 12 months	Primary: Changes in BMI, A1C, lipid profile, lipoprotein (a), homocysteine Secondary: Effect on FPG, PPG, HOMA index	Primary: No BMI change was observed at 3, 6, 9 and 12 months in either group. There was no difference in BMI value between pioglitazone and rosiglitazone. Significant A1C decreases were observed at 9 (both P<0.05 vs baseline) and 12 months (both P<0.01 vs baseline) in both groups. Significant TC, LDL cholesterol, HDL cholesterol, and TG improvement was present in the pioglitazone group at 12 months compared with the baseline values, and these variations were significantly different than rosiglitazone (P<0.05). No TC, LDL cholesterol, HDL cholesterol, or TG improvement was present in the rosiglitazone group after 12 months. Significant lipoprotein (a) and homocysteine improvement was present in the pioglitazone group at 12 months compared with the baseline values (both P<0.05), and lipoprotein (a) change was significant compared with the rosiglitazone group (P<0.05). Significant homocysteine decrease was observed in the rosiglitazone group at the end of the study (P<0.05). Secondary: After 9 and 12 months, mean FPG and PPG levels decreased in both groups compared to baseline (both P<0.05 and P<0.01, respectively). HOMA index improved in both groups at 12 months (P<0.05).
Berneis et al.[64] (2008) Pioglitazone 30 mg QD for 4 weeks, then 45 mg	RCT, XO Patients with type 2 diabetes for ≥6 months with a stable A1C (6.5% to 9.0%)	N=9 24 weeks of active treatment with an 8-week	Primary: Change in A1C, insulin sensitivity, and lipid parameters	Primary: The mean change in A1C from baseline to week 12 was -0.54% with pioglitazone and -0.59% with rosiglitazone (P=0.55). Insulin resistance decreased 14% with pioglitazone and 10% with rosiglitazone (P=0.51).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD for 8 weeks vs rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks All lipid-lowering medications were discontinued 4 weeks prior to the study.	and on a maximum of two oral antidiabetic drugs	wash-out period		There were no significant differences among the treatment groups in the following fasting lipid parameters: HDL-C (P=0.26), LDL-C (P=0.31), LDL size (P=0.51). Total cholesterol increased more after rosiglitazone compared with pioglitazone (+9% vs +3%; P=0.04). Triglycerides decreased after treatment with pioglitazone and increased after treatment with rosiglitazone (-21% vs +19%; P=0.004). The only postprandial lipid parameters that demonstrated a significant effect of pioglitazone compared to rosiglitazone was an increased LDL-IIB (+5% vs -4%; P=□0.01) and decreased LDL-IVB (-15% vs +10%; P=□0.05) after 3 hours. After 6 hours, there were no significant changes found.
Chappuis et al.[20] (2007) Pioglitazone 30 mg QD for 4 weeks, then 45 mg QD for 8 weeks vs rosiglitazone 4 mg QD for 4 weeks, then 4 mg BID for 8 weeks All lipid-lowering medications were discontinued 4 weeks prior to the study.	RCT, XO Patients with type 2 diabetes for ≥6 months with a stable A1C (6.5% to 9.0%) and on a maximum of two oral antidiabetic drugs	N=17 24 weeks of active treatment with an 8-week wash-out period	Primary: Change in A1C, FPG, insulin, insulin sensitivity, NEFA, and lipid parameters	Primary: Treatment with pioglitazone and rosiglitazone resulted in similar changes in A1C (−0.3% and −0.5%, respectively, P=0.43), FPG (−1.4 mmol/L and −1.6 mmol/L, respectively; P=0.68), fasting insulin concentrations (−3.9 mU/L and −8.2 mU/L, respectively; P=0.33), insulin sensitivity (−2.4 mmol/L × mU/L and −4.7 mmol/L × mU/L, respectively; P=0.33), and fasting NEFA concentrations (0.2 mmol/L and −0.5 mmol/L; P=0.25). Treatment with pioglitazone led to a reduction in fasting triglycerides compared to an increase with rosiglitazone (−0.35 mmol/L and+0.44 mmol/L, respectively; P=0.037). Treatment with pioglitazone did not change the fasting total cholesterol concentration, whereas there was an increase with rosiglitazone (+0.06 mmol/L and +0.59 mmol/L, respectively; P=0.031). Treatment with pioglitazone did not change the fasting VLDL-protein concentrations within the VLDL fractions, whereas rosiglitazone increased the protein content of VLDL-2 (−2.6 mg/dl and +17.7 mg/dL, respectively; P=0.035). There were no significant differences on apoB and apoA-I between the treatment groups. Treatment with pioglitazone led to a reduction in apoC-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				II concentrations compared to an increase with rosiglitazone (−0.1 mg/dl and +1.0 mg/dL, respectively; P=0.022). There was no significant difference in apoC-III (P=0.094) or the apoC-II/apoC-III ratio among the treatment groups. There was no difference in LPL and HL activity among patients receiving pioglitazone and rosiglitazone. CETP activity decreased after treatment with rosiglitazone and increased following treatment with pioglitazone (−6.2 pmol/mL/min and +4.6 pmol/mL/min, respectively; P<0.001). There was no difference in postprandial glucose and insulin concentrations between the treatment groups (P=0.944 and P=0.703, respectively). AUC of TG concentrations showed a significant difference between rosiglitazone and pioglitazone (P=0.017). AUC of NEFA concentrations was not significantly different among the treatment groups (P=0.610). The VLDL composition after 3 and 6 hours was significantly different following treatment with pioglitazone compared to rosiglitazone, favor of pioglitazone.
Pavo et al.[58] (2003) Pioglitazone 30 to 45 mg daily vs metformin 850 to 2,550 mg daily	DB, MC, RCT Recently diagnosed (<12 months) type 2 diabetic patients ≥40 years old, A1C of 7.5%-11%, and naïve to oral antihyperglycemic medications	N=205 32 weeks	Primary: Change in A1C from baseline Secondary: Changes in FPG, fasting serum insulin, and insulin sensitivity	Primary: Each treatment group had a significant reduction in A1C from baseline (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.280). Secondary: Each treatment group had a significant reduction in FPG (P<0.0001 for each group). The difference between pioglitazone and metformin was not significant (P=0.620). Pioglitazone reduced fasting serum insulin significantly (P<0.0001). The change in fasting serum insulin was not significant for metformin (P=0.803). Pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of homeostasis model assessment for insulin sensitivity (P=0.002).
Giles et al.[77] (2008)	RCT, DB, MC	N=518	Primary: Heart failure	Primary: Pioglitazone was associated with a higher incidence rate of the composite

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pioglitazone 30 to 45 mg QD vs glyburide 10 to 15 mg daily Insulin was the only rescue medication allowed.	Patients ≥18 years of age with type 2 diabetes, A1C ≥7.0%, body mass index ≤48 kg/m^2, New York Heart Association (NYHA) functional Class II/III heart failure (HF), left ventricular systolic dysfunction (LVEF ≤40%), and receiving sulfonylurea therapy (+/- insulin) for ≥30 days before screening or discontinued metformin therapy within 30 days of screening	6 months	progression (defined as the composite of CV mortality and hospitalization or ER visit for HF) and metabolic parameters	end point compared with glyburide (13.4% vs 8.2%, respectively; P=0.024). Death from CV cause was similar between the treatment groups (1.9% and 2.3% for pioglitazone and glyburide, respectively). Overnight hospitalization for HF was higher in the pioglitazone group (9.9%) compared to glyburide group (4.7%). ER visits for HF occurred in 1.5% of pioglitazone patients compared to 1.2% of glyburide patients. Echocardiographic data demonstrated preserved cardiac function with similar changes in the LVMI (P=0.959) and LVEF (P=0.413) among the treatment groups. Cardiac index was significantly increased with pioglitazone compared with glyburide (P=0.012). FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment. By week 16, a significant difference in mean FPG was observed favoring pioglitazone. At week 24, pioglitazone decreased the A1C by -0.98% compared to -0.73% with glyburide (P=0.007). At week 24, significant differences were seen between pioglitazone and glyburide in triglycerides (-36.8 mg/dl vs +7.6 mg/dl, respectively; P<0.001), HDL-C (+4.8 mg/dl vs -0.8 mg/dl, respectively; P<.001), and LDL-C (+6.9 mg/dl vs -2.4 mg/dl, respectively; P<0.016). Rates of adverse events and serious adverse events were similar between treatment groups. Hypoglycemia was more common with glyburide and edema was more common with pioglitazone. Weight gain was reported as an adverse event more frequently with pioglitazone than glyburide. (6.1% versus 2.7%, respectively). Mean weight gain was greater (2.10 kg vs 1.23 kg, respectively, P=0.012) with pioglitazone than with glyburide.
Kahn et al.[41] (2006)	DB, MC, RCT (ADOPT)	N=4,360 4 years	Primary: Time to monotherapy	Primary: The cumulative incidence of monotherapy failure at 5 years was 15% for rosiglitazone, 34% for glyburide and 21% with metformin. This represents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosiglitazone 4 mg QD to 4 mg BID vs glyburide 2.5 mg QD to 7.5 mg BID vs metformin 500 mg QD to 1 g BID	Patients 30-75 years of age recently diagnosed with type 2 diabetes with a FPG 126-180 mg/dL		failure (defined as FPG >180 mg/dL after an overnight fast on consecutive testing after at least 6 weeks of treatment at the maximum-dictated or tolerated dose of study drug) Secondary: Effect on FPG, A1C, weight, insulin sensitivity, β-cell function, adverse events	a risk reduction of 63% for rosiglitazone as compared with glyburide, and 32% for rosiglitazone as compared with metformin (P<0.001 for both comparisons). Secondary: The rate of progression to a confirmed FPG >140 mg/dL was significantly lower with rosiglitazone than glyburide (RR, 62%; 95% CI, 51 to 72; P<0.001) or metformin (RR, 36%; 95% CI, 15 to 52; P=0.002). At the 4-year evaluation, 40% of the patients in the rosiglitazone group had an A1C <7%, as compared with 26% for glyburide (P<0.001) and 36% for metformin (P=0.03). Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide (P<0.001 for all comparisons). During the first 6 months, insulin sensitivity increased more in the rosiglitazone group than in the metformin group. Thereafter, insulin sensitivity improved at similar rates in the two groups, with a significant difference between the 2 groups noted at 4 years (P<0.001). Insulin sensitivity did not change significantly in the glyburide group. During the first 6 months, levels of β-cell function increased more with glyburide than rosiglitazone or metformin. Thereafter, levels of β-cell function declined in all 3 groups. The annual rate of decline after 6 months was 6.1% for glyburide (P<0.001), 3.1% for metformin (P=0.02) and 2.0% for rosiglitazone. The number of deaths from all causes was similar in the three groups; however, adverse events differed among the groups. Glyburide was associated with a lower risk of cardiovascular events (MI, CHF and stroke) than was rosiglitazone (P<0.05), and the risk associated with metformin was similar to that with rosiglitazone. There was no significant difference in the risk for CHF with rosiglitazone compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				metformin (HR, 1.22; 95% CI, 0.66 to 2.26; P=0.52), but the risk was significantly higher with rosiglitazone than glyburide (HR, 2.20; 95% CI, 1.01 to 4.79; P=0.05). While there was no significant difference noted in men, significantly more women who received rosiglitazone (9.30%) than glyburide (3.47%) or metformin (5.08%) experienced fractures (both P<0.01).
Bolen et al.[40] (2007) Biguanides vs meglitinides vs thiazolidinediones vs alpha-glucosidase inhibitors vs second-generation sulfonylureas	MA Analysis of 216 controlled trials and cohort studies, and 2 systemic reviews that addressed benefits and harms of oral diabetes drug classes in patients with type 2 diabetes Studies were included if the drugs were not available in the US market if members of their class were in use and had not been banned (voglibose†, gliclazide*, and glibenclamide*), monotherapy therapies and combination therapies that are commonly used (metformin, second-generation sulfonylureas, and	N=136 (articles on intermediate outcomes) N=167 (articles on adverse events) N=68 (articles on microvascular outcomes and mortality) Variable duration	Primary: Intermediate outcomes: A1C level, body weight, blood pressure and lipid panels, all-cause mortality, cardiovascular morbidity and mortality and microvascular outcomes Secondary: Adverse events: hypoglycemia, gastrointestinal problems, congestive heart failure, edema or hypervolemia, lactic acidosis, elevated liver enzymes, allergic reactions requiring hospitalization and other serious adverse events	Primary: Results from clinical trials showed that most oral agents including thiazolidinediones, metformin, and repaglinide improved glycemic control to the same degree as sulfonylureas (absolute decrease in A1C level of about 1%). Nateglinide and alpha-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials. Thiazolidinediones were the only class with beneficial effect on HDL (mean relative increase, 3 to 5 mg/dL) but a harmful effect on LDL (mean relative increase, 10 mg/dL) compared with other oral agents. Metformin decreased LDL levels by about 10 mg/dL, whereas other oral agents had no effects on LDL. Thiazolidinediones, second-generation sulfonylureas, and metformin had similarly minimal effects on systolic blood pressure. Most agents except metformin increased body weight by 1 to 5 kg. In the ADOPT (A Diabetes Outcome Progression Trial), the incidence of cardiovascular events was lower with glyburide than with rosiglitazone or metformin (1.8%, 3.4%, and 3.2%, respectively; P<0.05). In the RECORD study (rosiglitazone evaluated for cardiac outcomes and regulation of glycemia in diabetes), rosiglitazone plus metformin or a sulfonylurea compared with metformin plus a sulfonylurea had a hazard ratio of 1.08 (95% CI, 0.89 to 1.31) for the primary end point of hospitalization or death from cardiovascular disease. The hazard ratio was driven by more congestive heart failure in the rosiglitazone plus metformin group than in the control group of metformin plus sulfonylurea

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	thiazolidinedione)			(absolute risk, 1.7% vs 0.8%, respectively). Too few comparisons were made to draw firm comparative conclusions on microvascular outcomes. Secondary: According to several randomized, controlled trials and some observational studies, sulfonylureas and repaglinide were associated with greater risk for hypoglycemia. In many randomized controlled trials, thiazolidinediones were associated with a higher risk for edema than sulfonylureas or metformin (absolute risk difference, 2% to 21%). In cohort studies, thiazolidinediones were associated with higher risk for congestive heart failure although absolute risks were small (1% to 3%) and higher risk for mild anemia yet produced similarly low rates of elevated aminotransferase levels (<1%) compared with sulfonylureas and metformin. In many trials and a few observational studies, metformin was associated with greater risk for gastrointestinal problems compared with other oral diabetes agents. According to a systematic review of 176 comparative trials, lactic acidosis events were similar between metformin and other oral diabetes agents.
Norris et al.[80] (2007) Pioglitazone vs rosiglitazone	MA Patients with metabolic syndrome, pre-diabetes, and type 2 diabetes receiving treatment with pioglitazone or rosiglitazone	N=14,290 (112 trials) Variable duration	Primary: A1C, lipids, weight, and adverse events	Primary: For pioglitazone, the between-group change in A1C was - 0.99% (95% CI, -1.18 to -0.81) and for rosiglitazone was -0.92% (95% CI, -1.2 to -0.64). Indirect comparison of pioglitazone and rosiglitazone found no significant difference in A1C (between-group difference -0.07% [95% CI, -0.41 to 0.27]). Rosiglitazone increased total cholesterol (13.70 mg/dl [95% CI, 1.06 to 26.35]) and pioglitazone decreased triglyceride levels (-1.08 mg/dl [95% CI, -2.08 to -0.09]). Using indirect comparisons, rosiglitazone increased total cholesterol compared to pioglitazone (net between-drug effect 13.91 mg/dl [95% CI, 1.20 to 26.62]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Data were insufficient to assess comparative effects of pioglitazone and rosiglitazone on microvascular and macrovascular events. Few data were available on the comparative effect of pioglitazone and rosiglitazone on cardiovascular risk factors among persons with pre-diabetes or the metabolic syndrome. There were insufficient data to determine whether pioglitazone and rosiglitazone have different effects on the incidence of diabetes among persons with either pre-diabetes or the metabolic syndrome. There was limited reporting of adverse events in the available head-to-head trials. Among 719 participants with type 2 diabetes and dyslipidemia, there were no differences between pioglitazone and rosiglitazone at 24-weeks follow-up for weight change (pioglitazone 2.0 kg and rosiglitazone 1.6 kg; P=0.164), liver function tests, creatinine phosphokinase, blood pressure, heart rate, hematocrit, hypoglycemic episodes, edema, or congestive heart failure. There were generally no differences in rates of adverse events between the active-treatment and placebo groups. The most frequently reported adverse events were edema, hypoglycemia, and weight gain. Both drugs increased weight compared to placebo: pioglitazone 2.96 kg (95% CI, 0.73 to 5.20) and rosiglitazone 2.12 kg (95% CI, 0.89 to 3.36), with no significant difference between the two drugs (95% CI, -1.71 to 3.39).
Type 2 Diabetes – Combination Therapy				
Chogtu et al.[81] (2009) Pioglitazone (variable doses) and glimepiride 2 mg daily vs rosiglitazone	RCT, OL Patients 30 to 70 years of age with type 2 diabetes mellitus who received glimepiride and required a thiazolidinedione due to a lack of glycemic control,	N=63 12 weeks	Primary: Blood glucose levels, plasma lipids and blood pressure at 12 weeks	Primary: The mean change in the fasting blood glucose (FBG) and postprandial blood glucose (PPBG) from baseline to week 12 was significant in both groups (P<0.05). There was no significant difference between the treatment groups with regard to the change in FPG (P=0.10) and PPBG (P=0.95). A1C levels also decreased from baseline to week 12. There was no significant difference between the treatment groups (P>0.05). At week 12, 37.9% of patients in the pioglitazone group and 17.8% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(variable doses) and glimepiride 2 mg daily	normotensive, and not on antilipemic therapy			rosiglitazone group had A1C <7.0%. Total cholesterol decreased in both treatment groups; however, to a greater extent with pioglitazone compared to rosiglitazone (P=0.004). Triglycerides in the pioglitazone group (P=0.0006) decreased significantly in comparison to the rosiglitazone group (P=0.255) at 12 weeks (P=0.002 pioglitazone vs rosiglitazone). LDL cholesterol decreased significantly (P=0.005) in the pioglitazone group compared to the rosiglitazone group. There was no significant difference in HDL cholesterol among the treatment groups (P>0.05). There was no change in systolic blood pressure with pioglitazone or rosiglitazone from baseline to week 12. There was also no significant difference in systolic blood pressure between the treatment groups (P=0.45). There was an increase in the weight following treatment with pioglitazone and rosiglitazone; however, there was no difference between the treatment groups (P=0.10).
Einhorn et al.[46] (2000) Pioglitazone 30 to 45 mg and metformin (existing therapy) vs metformin (existing therapy)	DB, RCT Patients with poorly controlled type 2 diabetes (A1C≥8%) with metformin monotherapy (baseline A1C was 9.86% for pioglitazone and 9.75% for placebo)	N=328 16 weeks	Primary: Effect on A1C, FPG, insulin, lipoproteins, and C-peptide	Primary: Reductions in A1C with pioglitazone add-on therapy were significantly lower compared to placebo (–0.83% difference between treatment groups; P≤0.05). Reductions in FPG with pioglitazone add-on therapy were significantly lower compared to placebo (–37.7 mg/dL difference between treatment groups; P≤0.05). Pioglitazone reduced fasting C-peptide levels (–0.1 ng/mL) while placebo increased levels (+0.1 ng/mL; P≤0.05). Pioglitazone reduced fasting C-insulin levels (–2.1 ng/mL) while placebo increased levels (+0.4 ng/mL; P<0.05). Pioglitazone add-on therapy significantly reduced TG (–9.7 vs +8.5 mg/dL; P≤0.05) and increased HDL cholesterol (10.2 mg/dL vs 1.5 mg/dL; P≤0.05) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both treatment groups increased LDL cholesterol (+7.7 mg/dL for pioglitazone and +11.9 mg/dL for placebo; P=NS). No significant difference between treatment groups in number of adverse events was observed. Higher rate of edema was reported with pioglitazone (5.9% vs 2.5%). Weight loss was observed with placebo (–1.36 kg) while patients receiving pioglitazone had weight gain (+0.95 kg).
Kaku et al.[74] (2009) Pioglitazone 15 to 30 mg QD and metformin 500 to 750 mg daily vs metformin 500 to 750 mg daily	RCT, DB, PC, PG Patients 20 to 65 years of age with type 2 diabetes, A1C 6.5% to 10%, who were drug naïve or on metformin monotherapy	N=169 28 weeks	Primary: A1C, fasting blood glucose (FBG), fasting insulin, insulin resistance, and lipid parameters	Primary: At week 28, mean change in A1C from baseline was -0.67% in the pioglitazone and metformin group compared to +0.25% in the metformin monotherapy group (P<0.0001). More patients receiving pioglitazone and metformin achieved an A1C <6.5% than patients in the metformin monotherapy group (38.6% vs. 8.1%, respectively; P<0.0001). At week 28, mean change in FBG from baseline was -20.5 mg/dl in patients receiving pioglitazone and metformin compared to +1.9 mg/dl in patients receiving metformin monotherapy (P<0.0001). Mean fasting insulin concentrations were reduced to a greater extent in the pioglitazone and metformin group (-2.15 mU/ml) compared to the metformin monotherapy group (-0.38 mU/ml; P=0.021). Insulin resistance was reduced more by pioglitazone and metformin than with metformin monotherapy (-1.34 vs. -0.15; P=0.0025). The main differences in lipids between pioglitazone and metformin combination therapy compared to metformin monotherapy were significant increases in total cholesterol (P=0.0057) and HDL-cholesterol (P<0.0001). Adiponectin levels were significantly increased by pioglitazone and metformin compared with metformin monotherapy (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Perez et al.[67] (2009) Pioglitazone/ metformin FDC 15 mg/850 mg BID vs pioglitazone 15 mg BID vs metformin 850 mg BID	RCT, DB, PG Patients ≥18 years of age with type 2 diabetes, A1C 7.5% to 10%, BMI ≤45 kg/m^2, who were drug naïve	N=600 24 weeks	Primary: Change in A1C from baseline to final visit or early termination Secondary: A1C responder rate, changes from baseline to week 24 (or early termination) in FPG, fasting insulin, and insulin resistance	Primary: At week 24, mean change in A1C from baseline was -1.83% in the pioglitazone/ metformin FDC group compared to -0.96% pioglitazone and -0.99% for metformin (P<0.0001 for the FDC group compared to each monotherapy group). Secondary: In the pioglitazone/metformin FDC group, 63.8% achieved A1C <7% compared with 46.9% in the pioglitazone and 38.9% in the metformin monotherapy group. Treatment with pioglitazone/metformin FDC led to the greatest reduction in FPG from baseline to final visit (-39.9 mg/dL) compared to -22.2 mg/dL for pioglitazone monotherapy and -24.8 mg/dL for metformin monotherapy (P<0.01 for the FDC group compared to each monotherapy group). Treatment with pioglitazone/metformin FDC led to the greatest reduction in fasting insulin from baseline to final visit (-3.91 µIU/mL), followed by pioglitazone monotherapy (–3.18 µIU/mL). Both reductions were significantly greater than with metformin monotherapy (-0.98 µIU/mL; P<0.05). At week 24, the greatest decrease in insulin resistance was seen in those patients receiving pioglitazone/metformin FDC and pioglitazone monotherapy compared to metformin monotherapy; however, the difference was significant only with pioglitazone/metformin FDC (P<0.01).
Kipnes et al.[55] (2001) Pioglitazone 15 to 30 mg and sulfonylurea (existing therapy) vs	DB, MC, PC, RCT Patients on a stable regimen of a sulfonylurea for ≥30 days with an A1C ≥8.0%, fasting C-peptide >1.0 ng/mL, BMI 25 to 45 kg/m^2	N=560 16 weeks	Primary: Change in A1C, FPG, TG, lipoproteins	Primary: Patients receiving pioglitazone and a sulfonylurea had significant decreases (P<0.05) from baseline in A1C and FPG levels compared to patients in the placebo and sulfonylurea group. Both pioglitazone and sulfonylurea groups had significant (P<0.05) mean percent decreases in TG levels (17%; 95% CI, 6% to 27% for 15 mg and 26%; 95% CI, 16% to 36% for 30 mg) and increases in HDL cholesterol levels (6%; 95% CI, 1% to 11% for 15 mg and 13%; 95% CI, 8% to 18%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfonylurea (existing therapy)				for 30 mg) compared with placebo and sulfonylurea. There were small but statistically significant (P≤0.05) mean percent increases in LDL cholesterol levels in all groups. The adverse event rates were similar in all groups.
Matthews et al.[60] (2005) Pioglitazone 15 to 45 mg QD and metformin (existing therapy) vs gliclazide* 80 to 320 mg QD and metformin (existing therapy)	DB, RCT Patients with type 2 diabetes that was poorly controlled (A1C 7.5%-11%) with metformin monotherapy	N=630 12 months	Primary: Effect on A1C Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in A1C were observed in pioglitazone- (–0.99%) and gliclazide-treated groups (–1.01%; P=0.837). Secondary: Similar reductions in FPG were observed in pioglitazone- (–2.1 mmol/L) and gliclazide- (–1.6 mmol/L) treated groups (P=0.506). Gliclazide significantly reduced LDL cholesterol compared to pioglitazone (–4.2 mg/dL vs +10.4 mg/dL; P=0.001). Pioglitazone significantly reduced TG (–53.1 vs –19.5 mg/dL; P<0.001) and increased HDL cholesterol (6.9 mg/dL vs no change; P<0.001) compared to gliclazide.
Charbonnel et al.[61] (2005) Pioglitazone 15 to 45 mg QD and metformin (existing therapy) vs gliclazide* 80 to 320 mg QD and metformin (existing therapy)	DB, RCT Patients with type 2 diabetes that was poorly controlled (A1C 7.5%-11%) with metformin monotherapy	N=630 24 months	Primary: Effect on A1C Secondary: Effect on FPG, insulin, lipoproteins, and C-peptide	Primary: Similar reductions in A1C were observed with pioglitazone add-on therapy (–0.89%) and with gliclazide add-on therapy (–0.77%; P=0.200) after 2 years. Secondary: Significant reductions in FPG were observed with pioglitazone add-on therapy (–1.8 mmol/L) compared to gliclazide add-on therapy (–1.1 mmol/L; P<0.001) after 2 years. Gliclazide add-on therapy had significantly reduced LDL cholesterol compared to pioglitazone add-on therapy (–6 mg/dL vs +2 mg/dL; P<0.001). Pioglitazone add-on therapy significantly reduced TG (–23 vs –7 mg/dL; P<0.001) and increased HDL cholesterol (22 mg/dL vs 7 mg/dL; P<0.001) compared to gliclazide add-on therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No significant difference between treatment groups in number of adverse events or discontinuation due to adverse events was reported. Less weight gain was observed with gliclazide add-on therapy to metformin (1.2 kg) compared to pioglitazone add-on therapy (2.5 kg).
Hanefeld et al.[62] (2004) Pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy) vs metformin 850 to 2,250 mg daily and sulfonylurea (existing therapy)	DB, MC, PG, RCT Patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy	N=639 12 months	Primary: Change in A1C Secondary: FPG, FPI, lipids, urinary albumin and creatinine (to determine albumin-to-creatinine ratio)	Primary: A1C was reduced by 1.20% and 1.36% in the pioglitazone and metformin groups, respectively (P=0.065 for differences between treatments). Secondary: FPG (P=0.528) and FPI (P=0.199) were also reduced but the between-treatment differences were not statistically significant. Pioglitazone addition to sulfonylurea significantly reduced TG (–16% vs –9%; P=0.008) and increased HDL cholesterol (14% vs 8%; P<0.001) compared with metformin addition. LDL cholesterol was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to sulfonylurea monotherapy (P<0.001). Urinary albumin-to-creatinine ratio was reduced by 15% in the pioglitazone group and increased 2% in the metformin group (P=0.017). Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group.
Comaschi et al.[79] (2008) Pioglitazone 15 to 30 mg QD as add-on to existing oral hypoglycemic therapy (either metformin or sulfonylurea)	RCT, OL, MC, PG Patients aged ≥35 years with type 2 diabetes who had received treatment with a stable dose of either metformin or a sulfonylurea as monotherapy for at least 3 months	N=250 6 months	Primary: Change in A1C from baseline to 6 months Secondary: Change in lipid profiles after 6 months of treatment	Primary: Pioglitazone-based and fixed-dose metformin/glibenclamide resulted in similar reductions in A1C (-1.11% vs. -1.29%, respectively; P=0.192) and FPG (-2.13 mmol/L vs. -1.81 mmol/L, respectively; P=0.370). Secondary: No changes in total cholesterol were observed with pioglitazone-based therapy (-0.017 mmol/L) compared to the fixed-dose combination of metformin/glibenclamide (-0.099 mmol/L; P=0.479). The addition of pioglitazone to metformin or a sulfonylurea led to a slight

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs metformin/ glibenclamide‡ FDC 400/2.5 mg 1-3 tablets daily	before study entry, A1C between 7.5% and 11%, and fasting C-peptide >0.33 nmol/L			increase in HDL-C (+0.04 mmol/L) compared to a reduction in HDL-C with metformin/glibenclamide (-0.09 mmol/L; P<0.001). There was no significant change in non-HDL-C in patients treated with pioglitazone-based therapy (-0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.01 mmol/L; P=0.677). There was no significant change in LDL-C in patients treated with pioglitazone-based therapy (+0.06 mmol/L) or the fixed-dose combination of metformin/glibenclamide (-0.03 mmol/L; P=0.425) There was a significant reduction in triglycerides with pioglitazone-based therapy (-0.25 mmol/L) compared to no change with the fixed-dose combination of metformin/glibenclamide (0.03 mmol/L; P=0.045).
Seufert et al.[70] (2008) <u>Study 1</u> Pioglitazone 15 to 45 mg QD and metformin (existing therapy) vs gliclazide* 80 to 320 mg daily and metformin (existing therapy) <u>Study 2</u> Pioglitazone 15 to 45 mg QD and sulfonylurea (existing therapy) vs	Two RCT, MC Patients 35 to 75 years of age with type 2 diabetes who were inadequately controlled on either metformin or sulfonylurea monotherapy (A1C 7.5% to 11.0%), and fasting C-peptide >1.5 ng/ml)	N=1,269 104 weeks	Primary: Change in A1C from baseline, FPG, glucose excursions using 3-h OGTT, and insulin sensitivity	Primary: <u>Study 1</u> The mean change in A1C from baseline to week 104 was -0.89% with pioglitazone and metformin compared to -0.77% with gliclazide and metformin (P=0.20). The mean change in FPG from baseline to week 104 was -1.8 mmol/l with pioglitazone and metformin compared to -1.1 mmol/l with gliclazide and metformin (P<0.001). Pioglitazone therapy in patients failing metformin therapy achieved decreases in glucose excursions at the end of the 2-year treatment period. This effect was not seen in the patients receiving gliclazide for 2 years as add-on therapy to failing metformin. Insulin sensitivity increased when pioglitazone was added to metformin therapy (+13.8%) compared with a decrease when gliclazide was added to metformin (-7.2%; P<0.0001). <u>Study 2</u> The mean change in A1C from baseline to week 104 was -1.03% for patients receiving pioglitazone and sulfonylurea compared to -1.16% for patients receiving metformin and sulfonylurea (P=0.173).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin 850 to 2,550 mg daily and sulfonylurea (existing therapy)				The mean change in FPG from baseline to week 104 was -2.0 mmol/l with pioglitazone and sulfonylurea compared to -1.9 mmol/l with metformin and sulfonylurea (P=0.506). The addition of pioglitazone to failing sulfonylurea therapy for 2 years resulted in a decrease of post-load glucose excursions which was not seen when metformin was added to sulfonylurea treatment. Insulin sensitivity increased when pioglitazone was added to sulfonylurea, (+5.8%) compared to an increase of +3.9% when metformin was added to sulfonylurea (P=0.581 between treatments).
Aljabri et al.[39] (2004) Pioglitazone 30 to 45 mg QD and existing sulfonylurea or metformin therapy vs NPH insulin 0.3 unit/kg once daily at bedtime and existing sulfonylurea or metformin therapy	OL, RCT Patients with poorly controlled type 2 diabetes (A1C >8%) with insulin secretagogues and metformin monotherapy	N=62 16 weeks	Primary: Effect on A1C, FPG, incidence of hypoglycemia (< 68 mg/dL), effect on lipoproteins, quality of life (assessed using the Diabetes Treatment Satisfaction Questionnaire)	Primary: Similar reductions in A1C were observed in pioglitazone-treated (–1.9%) and NPH insulin-treated patients (–2.3%; P=0.32). Nonsignificant differences in reduction in FPG were observed with NPH insulin (–77 mg/dL) and pioglitazone (–52 mg/dL; P=0.07). Significantly more patients reported hypoglycemia with NPH insulin (19) than with pioglitazone (11; P=0.02). Significant increases in HDL cholesterol were observed with pioglitazone (4 mg/dL) compared to NPH insulin (0 mg/dL; P=0.02). No significant differences in total cholesterol, LDL cholesterol and triglycerides were reported between the two treatment groups. No significant differences were noted for the Diabetes Treatment Satisfaction Questionnaire scores between the two treatment groups.
Dorkhan et al.[72] (2008) Pioglitazone 30 to 45 mg QD and existing oral hypoglycemic	RCT, OL Patients with type 2 diabetes and inadequate glycemic control (defined as treatment	N=36 26 weeks	Primary: Change in A1C, β-cell function, insulin sensitivity, degree of patient satisfaction	Primary: After 26 weeks, the change in A1C from baseline was -1.3% (P<0.01) for pioglitazone and -2.2% (P<0.01) for insulin glargine. There was no significant difference between the treatment groups (P=0.050). There was no difference in insulin, β-cell function, or insulin sensitivity among the two treatment groups (P=NS). Insulin glargine resulted in a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy vs insulin glargine 6-10 IU/day administered in the morning (titrated as necessary) and existing oral hypoglycemic therapy	with metformin and sulfonylurea/ meglitinide in doses ≥50% of maximum recommended doses and A1C >6.2%			greater reduction in proinsulin concentrations than pioglitazone (-55% vs. -25%; P<0.01). Pioglitazone increased HDL-C (0.14 mmol/L) compared to a slight decrease in the insulin glargine group (-0.04 mmol/L; P<0.01 between groups). There were no significant differences between the treatment groups with regards to other lipid parameters (P=NS). The degree of satisfaction with treatment was similar in the pioglitazone and insulin glargine treatment groups. There was a doubling of serum adiponectin levels in the pioglitazone group (7.5 to 15; P<0.01) compared to a significant decrease in the insulin glargine group (8.7 to 7.6; P=0.04; P<0.01 between groups).
Ligvay et al.[75] (2009) Pioglitazone 15 to 45 mg QD, metformin 1,000 mg BID, and glyburide 1.25 mg BID vs insulin aspart protamine and insulin aspart (NovoLog Mix 70/30) 0.2 units/kg divided twice daily and metformin 1,000 mg BID Doses of medications could	RCT, OL Patients 21 to 70 years of age with type 2 diabetes who were treatment naïve	N=58 36 months	Primary: A1C, rate of treatment failures (defined as A1C >8%), hypoglycemia, weight gain, compliance, QoL, and patient satisfaction	Primary: After 36 months, A1C was 6.1 % in the insulin-treated group compared to 6.0% in the triple oral group (P=0.26). The percentage of patients achieving A1C <7.0% was 100% in both groups at baseline; 92% of patients in the insulin group and 76% of patients in the triple oral group met the A1C goal at the end of 36 months. Three patients in each group reached the “treatment failure” end point. The insulin group had 0.51 mild hypoglycemia events/person month and the triple oral group had 0.68 event/person-month (P=0.18). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/ person-year (P=0.53). In the completer analysis, the triple oral group experienced more weight gain than the insulin group: 10.10 kg (95% CI, 4.46 to 15.74) versus 3.36 kg (-0.47 to 7.20; P=0.04). Compliance was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group. There were differences between the groups for any of the 12 QoL domains

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
be titrated at the investigator's discretion.				evaluated. All patients receiving insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization.
Fonseca et al.[50] (2000) Rosiglitazone 4 mg and metformin 2,500 mg daily vs rosiglitazone 8 mg and metformin 2,500 mg daily vs metformin 2,500 mg daily	DB, PC, RCT Patients with poorly controlled type 2 diabetes (mean FPG 140 to 300 mg/dL) with metformin (baseline A1C was 8.6% in the metformin treatment group, 8.9% in the rosiglitazone 4 mg-metformin 2,500 mg treatment group and 8.9% in the rosiglitazone 8 mg-metformin 2,500 mg treatment group)	N=348 26 weeks	Primary: Effect on A1C, FPG, fructosamine, C-peptide, FFA, lipids, lactate, and estimates of insulin sensitivity (HOMA-S) and β-cell function (HOMA-B)	Primary: Addition of rosiglitazone significantly reduced A1C in a dose-related fashion from baseline compared to metformin monotherapy. Mean difference from the metformin control group was –1.0% (P<0.001) with rosiglitazone 4 mg-metformin 2,500 mg and –1.2% with rosiglitazone 8 mg-metformin 2,500 mg (P<0.001). Mean FPG concentrations were reduced significantly with rosiglitazone 4 mg-metformin 2,500 mg (–33 mg/dL; P<0.0001) and with rosiglitazone 8 mg-metformin 2,500 mg (–48.4 mg/dL; P<0.0001). No significant change in FPG was observed with metformin monotherapy. Fructosamine levels were reduced with both rosiglitazone 4 mg-metformin 2,500 mg (–27.9 μmol/L) and 8 mg-metformin 2,500 mg (–36.8 μmol/L). Fructosamine levels increased with metformin monotherapy (+12.3 μmol/L). C-peptide values were reduced significantly in all treatment groups compared to baseline (P<0.05). FFA levels were significantly less in both rosiglitazone-metformin treatment groups compared to metformin monotherapy (P<0.05). Significant increases in TC, HDL cholesterol and LDL cholesterol were observed with both rosiglitazone groups when compared to metformin monotherapy (P<0.05). Mean fasting lactate levels were significantly less in both rosiglitazone-metformin treatment groups compared to metformin monotherapy (P<0.05). Both insulin sensitivity (as measured by HOMA-S) and β-cell function (as measured by HOMA-B) were increased in a dose-dependent fashion with

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				rosiglitazone-metformin combination compared to metformin monotherapy.
Weissman et al.[52] (2005) Rosiglitazone 8 mg QD and metformin 1,000 mg/day (RSG + MET) vs metformin 1,500 mg/day (MET)	DB, MC, PG, RCT Patients 18-75 years of age diagnosed with type 2 diabetes (defined as A1C of 6.5%-8.5% for patients receiving combination therapy with metformin and sulfonylurea or A1C of 7%-10% for drug-naïve or patients receiving monotherapy), FPG of 126-270 mg/dL and BMI ≥27kg/m^2	N=766 24 weeks	Primary: Mean change from baseline A1C after 24 weeks of treatment Secondary: Mean change from baseline FPG at week 24 and proportion of patients responding to treatment, defined as reduction of ≥0.7% for A1C and ≥30 mg/dL for FPG at week 24, clinical safety, adverse events, tolerability and clinical laboratory tests	Primary: After 24 weeks, RSG + MET combination therapy and MET monotherapy were both effective in improving A1C with mean reductions of –0.93% (95% CI, –1.06% to –0.80%) and –0.71% (95% CI, –0.83% to –0.60%), respectively, with a mean treatment difference of –0.20% (95% CI, –0.36% to –0.04%). Secondary: Significant reductions in FPG from baseline were seen in patients receiving MET + RSG (–2.29 mmol/L; 95% CI, –2.59 mmol/L to –1.99 mmol/L) compared to patients receiving MET monotherapy (–1.12 mmol/L; 95% CI, –1.43 mmol/L to –0.82 mmol/L), with a treatment difference of –0.85 mmol/L (95% CI, –1.23 mmol/L to –0.47 mmol/L). The proportion of patients who responded to treatment (reduction in A1C ≥0.7%) was greater in the RSG + MET group than the MET monotherapy group (59.5% and 49.5%, respectively) with the treatment difference of 10% (95% CI, 1.9% to 18.1%). The proportion of FPG responders (reduction in FPG ≥30 mg/dL) was also greater in the RSG + MET group than in the MET monotherapy group (55% vs 32.5%, respectively). The percentage of patients experiencing a gastrointestinal effect was greater in the MET group compared with the RSG + MET group (38.7% and 27.9%). The odds of experiencing a gastrointestinal side effect were 63% greater for patients receiving MET monotherapy compared to RSG + MET combination therapy (OR, 1.63; 95% CI, 1.19 to 2.24). RSG + MET resulted in a mean weight gain of 1.79 kg (P<0.0001) compared with a mean weight loss of 1.78 kg (P<0.001) on MET monotherapy. There were 3 deaths during the course of the study with 2 prior to double-blind study medication, and 1 while on RSG + MET; the cause of which

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was unknown, although it was not considered to be treatment related.
Stewart et al.[53] (2006) Rosiglitazone 8 mg QD and metformin 2,000 mg/day (MET + RSG) vs metformin 3,000 mg/day (MET)	DB, MC, PG, RCT Type 2 diabetic patients aged 18-70 years, who were either antidiabetic-drug-naïve with FPG of 7.0-9.0 mmol/L and A1C 7.0%-9%, or previously treated with oral antidiabetic monotherapy with FPG of 6.0-8.0 mmol/L and A1C 6.5%-8.0%	N=526 32 weeks	Primary: Proportion of patients achieving A1C ≤6.5% at week 32 and the change in A1C from baseline to week 32 Secondary: Proportion of patients achieving target A1C and FPG levels, change in FPG and fasting plasma insulin from baseline to week 32, change in insulin resistance, pancreatic β-cell function, CRP, lipid parameters and 24-hour ambulatory blood pressure, safety and tolerability	Primary: There was a reduction from baseline in mean A1C in the MET + RSG group from 7.2% to 6.7% compared with 7.2% to 6.8% in the MET group (P=0.0357) at week 32. Secondary: The proportion of patients achieving A1C ≤6.5% at week 32 was similar in the two groups (P=0.095). The proportion of patients achieving FPG <7.0 mmol/L at week 32 was 56% in the MET + RSG group compared with 38% in the MET group (OR, 2.33; P<0.0001). The reduction in fasting plasma insulin from baseline was greater in the MET + RSG group compared with the MET group (treatment difference of –12.2 pmol/L; P=0.00029). Homeostasis model assessment estimated that insulin sensitivity, β-cell function, CRP and systolic blood pressure were greater in the MET + RSG group at week 32 compared with the MET group (P<0.05 for all). TC, HDL and LDL increased, free fatty acids decreased and TG did not change in the MET + RSG group, whereas in the MET group there were decreases in TC, LDL and TG and increases in HDL and free fatty acids. The difference between the treatments was statistically significant for the above parameters (P<0.05). The proportion of patients with reductions in 24-hour mean systolic blood pressure was greater in the MET + RSG group compared with the MET group (treatment difference of –3.6 mm Hg; P=0.0315). The overall incidences of gastrointestinal adverse events were comparable between groups, but there was a lower incidence of diarrhea in the MET + RSG group (8% vs 18%). Hypoglycemia was reported in 17 patients (7%) in the MET + RSG group compared with 10 patients (4%) in the MET group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were greater reductions in mean hemoglobin and hematocrit over 32 weeks in the MET + RSG group compared with the MET group (P<0.0001).
Rosak et al.[51] (2005) Rosiglitazone 4 to 8 mg and metformin (existing therapy)	OS, PM Two post marketing observational studies in which type 2 diabetics on metformin therapy received rosiglitazone add-on therapy (baseline A1C was 8.1% in both studies)	N=11,014 6 months	Primary: Effect on A1C, FPG, body weight and blood pressure from baseline	Primary: Addition of rosiglitazone significantly reduced A1C from baseline (–1.3%; P<0.0001). Addition of rosiglitazone significantly reduced FPG from baseline (–47.0 mg/dL; P<0.0001). Significant reduction in blood pressure from baseline (–7/–3 mm Hg; P<0.0001) was observed with rosiglitazone add-on therapy. Significant reduction in weight (–1.7 kg; P<0.0001) was observed with rosiglitazone add-on therapy. Most commonly reported adverse events were weight gain (0.16%) and edema (0.15%).
Bailey et al.[49] (2005) Rosiglitazone/ metformin FDC 4 mg/1,000 mg to 8 mg/2,000 mg daily vs metformin 2,500 to 3,000 mg daily	DB, MC, PG, RCT Patients with type 2 diabetes poorly controlled (FPG ≥126 to 216 mg/dL) with metformin alone or in combination with an insulin secretagogue or acarbose Baseline A1C was 7.4% for pioglitazone add-on therapy and 7.5% for metformin.	N=568 24 weeks	Primary: Effect on A1C Secondary: Effect on FPG, insulin, and proportion of patients who achieved A1C and FPG targets	Primary: Reductions in A1C observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (–0.22% difference between treatment groups; P=0.001). Secondary: Reductions in FPG observed with rosiglitazone add-on therapy were significantly lower compared to metformin monotherapy (–18.3 mg/dL difference between treatment groups; P<0.001). Significant reduction in fasting insulin was observed with rosiglitazone add-on therapy compared to metformin monotherapy (–12.4 pmol/L difference between treatment groups; P=0.001). Greater proportion of patients on pioglitazone (54%) reached A1C targets (<7%) compared to metformin monotherapy (36%; OR, 2.42; P<0.001). Greater proportion of patients on rosiglitazone (32%) reached FPG targets

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(<126 mg/dL) compared to metformin monotherapy (8%; OR, 5.71; P<0.001). Higher rate of withdrawal due to adverse events with metformin monotherapy (8% vs 4%) was noted. Gastrointestinal (GI) disorders were the most commonly reported event that caused withdrawal in the metformin group.
Rosenstock et al.[48] (2006) Rosiglitazone/ metformin FDC 4 mg/1,000 mg to 8 mg/2,000 mg daily vs rosiglitazone 4 to 8 mg daily vs metformin 500 to 2,000 mg daily	DB, MC, RCT Type 2 diabetics with A1C >7.5% to 11% with FPG ≤270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening	N=468 32 weeks	Primary: Change in A1C Secondary: Proportion of patients achieving A1C and FPG targets, change from baseline in FPG, FFA, lipids, insulin, insulin sensitivity (HOMA-S), C-reactive protein, adiponectin	Primary: Patients receiving rosiglitazone-metformin showed significant improvements in A1C with a reduction of 2.3% compared to baseline vs 1.8% for metformin (P<0.0008) and 1.6% with rosiglitazone (P<0.0001). Secondary: Target A1C ≤6.5% and <7% were achieved in more patients in the rosiglitazone-metformin group (60% and 77%) than with metformin (39% and 57%) or rosiglitazone (35% and 58%), respectively. The greatest mean decrease in FPG was seen with rosiglitazone-metformin (74 mg/dL) and was significant compared with metformin (50 mg/dl; P<0.0001) and rosiglitazone (47 mg/dl; P<0.0001). Treatment was well tolerated with nausea, vomiting and diarrhea as the most commonly reported adverse events. Edema was comparable between rosiglitazone-metformin (6%) and rosiglitazone (7%) and lower in the metformin group.
Hamann et al.[65] (2008) Rosiglitazone/ metformin FDC 4 mg/2,000 mg daily (RSG+MET) vs glibenclamide‡	RCT, DB, PG Overweight patients (BMI ≥25 kg/m^2) with type 2 diabetes, A1C 7% to 10%, who received metformin ≥850 mg/day for at least 8 weeks	N=596 52 weeks	Primary: Change in A1C from baseline to week 52 Secondary: Change in FPG, β-cell function, insulin resistance, hypoglycemia, blood pressure	Primary: At week 52, mean change in A1C from baseline was -0.78% for RSG+MET compared to -0.86% with SU+MET (95% CI, -0.08 to 0.25). Secondary: Reductions in FPG from baseline to week 52 was -2.29 mmol/L with RSG+MET compared to -2.25 mmol/L with SU+MET (P=0.8095). The degree of β-cell failure was significantly greater with SU+MET compared to RSG+MET as measured by the coefficient of failure (0.543 vs. 0.055 A1C%/year, respectively; P=0.0002).

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5 mg and metformin 2,000 mg or gliclazide* 80 mg and metformin 2,000 mg daily (SU+MET)				Insulin sensitivity increased 55% with RSG+MET compared to 12.3% with SU+MET (P<0.0001). Hypoglycemia occurred in 30% of patients receiving SU+MET compared to 6% of patients receiving RSG+MET (P<0.0001). After 52 weeks, 24-hour diastolic and systolic ambulatory blood pressures (ABP) were reduced with RSG+MET, but not with SU+MET. The difference between treatments was significant for diastolic ABP (-2.9 mmHg; P=0.0013), but not for systolic ABP (-2.6 mmHg; P=0.0549).
Rosenstock et al.[47] (2006) Rosiglitazone/ metformin FDC 4 mg/1,000 mg to 8 mg/2,000 mg daily	MC, OL Type 2 diabetics with A1C >11% or FPG >270 mg/dL who were previously treated with diet and exercise or had not been treated with a glucose-lowering agent for more than 15 days within 12 weeks prior to screening	N=190 24 weeks	Primary: Change in A1C Secondary: Proportion of patients achieving A1C targets, change in FPG, lipids, insulin sensitivity (HOMA-S)	Primary: Clinically significant mean reductions in A1C (11.8% to 7.8%; P<0.0001) were observed after initiation of rosiglitazone-metformin at week 24. Secondary: Treatment goals of A1C ≤6.5% and <7% at week 24 were achieved in 33% and 44% of patients, respectively. Clinically significant mean reductions in FPG (304 to 166 mg/dL; P<0.0001) were observed after initiation of rosiglitazone-metformin at week 24. HDL cholesterol increased 4.4% and TC (–3.7%), LDL cholesterol (–0.7%) and TG (–13.4%) decreased compared to baseline. The rosiglitazone-metformin fixed-dose combination product significantly increased HOMA estimates of insulin sensitivity by 68% (P<0.0001). The rosiglitazone-metformin fixed-dose combination was well tolerated. There was a 2% incidence of hypoglycemia, mean increase in weight of 2.6 kg from baseline and 2.6% of patients withdrew because of an adverse event.
Fonseca et al.[83] (2003) Rosiglitazone 8	DB, MC, PC, RCT Patients ≥21 years old with type 2	N=402 24 weeks	Primary: Change in A1C from baseline	Primary: A1C did not change significantly from baseline in the placebo plus rosiglitazone group, but did change significantly in the nateglinide plus rosiglitazone group. The change from baseline to end point was –0.8%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD and nateglinide 120 mg before each meal vs rosiglitazone 8 mg QD and placebo	diabetes diagnosed at least 6 months previously and treated with rosiglitazone 8 mg daily, diet, and exercise for at least 3 months, had a BMI between 22-40 kg/m^2, FPG between 6.1 and 13.3 mmol/L, and A1C of 7%-11%		Secondary: FPG, 2-hour postprandial insulin, TC, LDL, HDL, TG, body weight, 4-hour AUC for glucose and insulin during meal challenges	(P<0.0001 vs baseline or placebo plus rosiglitazone group). Secondary: Change in FPG decreased significantly from a baseline of 9.8 to 9.0 mmol/L in the nateglinide plus rosiglitazone group (P<0.001). FPG did not change significantly from the baseline (10 mmol/L) in patients receiving placebo plus rosiglitazone. 2-hour postprandial insulin in the nateglinide plus rosiglitazone group decreased from 14 to 11.4 mmol/L (P<0.0001). The group receiving placebo plus rosiglitazone had an increase in 2-hour postprandial insulin from 14.4 to 14.8 mmol/L (P<0.0001 vs combination). Total and incremental glucose $AUCs_{(0\text{-}4\ hours)}$ were significantly reduced in the nateglinide plus rosiglitazone group (–8.6 ±0.8 and –6.2 ±0.5 mmol/L/h, respectively; P<0.0001 vs baseline or placebo plus rosiglitazone for both total and incremental AUCs). This represents a 16% reduction in the total and a 49% reduction in the incremental glucose AUC. Total and incremental insulin $AUCs_{(0\text{-}4\ hour)}$ were increased in the nateglinide plus rosiglitazone patients (+425 ±37 and +395 ± pmol/L/h, respectively; P<0.0001 vs baseline or placebo plus rosiglitazone for both total and incremental AUCs). This represents a 46% increase in the total and 69% increase in the incremental insulin AUC. There were no statistically significant changes in TC, LDL, or TG in either group. There was a small, but significant increase from baseline in HDL seen in patients receiving nateglinide plus rosiglitazone (P<0.025) and the patients receiving placebo and rosiglitazone (P<0.005). Body weight increased in both groups. The mean change from baseline in patients receiving nateglinide plus rosiglitazone (+3.1 ±0.3 kg) was significantly greater than in patients in the placebo plus rosiglitazone group (+1.1 ±0.3 kg; P<0.0001). Meal challenges were performed at week 0 and at end point. The glucose

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and insulin profiles were similar in the two groups at baseline, and PPG and insulin concentrations were unchanged at end point relative to baseline in patients receiving placebo plus rosiglitazone.
Raskin et al.[84] (2004) Rosiglitazone 2 to 4 mg BID and repaglinide 0.5 to 4 mg TID before meals vs rosiglitazone 2 to 4 mg BID vs repaglinide 0.5 to 4 mg TID before meals	MC, OL, PG, RCT Patients ≥18 years old with type 2 diabetes for at least 12 months with an A1C>7% to ≤12% during previous monotherapy with sulfonylurea or metformin for at least 3 months with a BMI ≤45 kg/m^2	N=252 24 weeks	Primary: Change in A1C from baseline Secondary: Change in FPG from baseline	Primary: Mean change in A1C from baseline for repaglinide was –0.17% and –0.56% for rosiglitazone. The mean change in A1C from baseline for repaglinide plus rosiglitazone was –1.43 (P≤0.001 vs either monotherapy). The reduction in A1C from baseline was greater for the combination group than the sum of the responses for the monotherapy groups (P<0.01). Secondary: Mean FPG change from baseline for the repaglinide group was –3 mmol/L and –3.7 mmol/L for the rosiglitazone group. Mean FPG change from baseline for the repaglinide plus rosiglitazone group was –5.2 mmol/L (P≤0.001 vs either monotherapy).
McCluskey et al.[57] (2004) Rosiglitazone (existing therapy) and glimepiride 2 to 8 mg QD vs rosiglitazone (existing therapy)	MC, PC, RCT Patients with type 2 diabetes poorly controlled (A1C 7.5%-9.5%) with rosiglitazone monotherapy	N=40 30 weeks	Primary: Effect on A1C Secondary: Effect on FPG, body weight, lipoproteins and proportion of patients who achieved A1C and FPG targets	Primary: Significant reductions in A1C were observed with glimepiride add-on therapy (–1.2%) compared to placebo (–0.3%; P<0.001). Secondary: Significant reductions in FPG were observed with glimepiride add-on therapy (–24.41 mg/dL) than with placebo add-on therapy (+5.9 mg/dL; P<0.008). Significantly greater proportion of patients on glimepiride add-on therapy achieved the target A1C of ≤7% (60% vs 14.3%; P<0.008). There were no significant differences between treatment groups in total cholesterol, HDL cholesterol, LDL cholesterol or TG at any time during study period.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosenstock et al.[68] (2008) Study A Rosiglitazone 4 mg QD and glimepiride 3 mg QD (RSG 4 mg + GLIM) vs rosiglitazone 8 mg QD and glimepiride 3 mg QD (RSG 8 mg + GLIM) vs glimepiride 3 mg QD (GLIM alone) Study B Rosiglitazone 4 mg QD and glimepiride 2 to 4 mg QD (RSG add-on) vs glimepiride 4 to 8 mg QD and placebo (GLIM)	Two RCT, DB, PC Patients 40 to 80 years of age (study A) or 18 to 75 years of age (study B) with type 2 diabetes, A1C ≥7.0% and FPG 126–270 mg/dl at baseline. In the 3 months prior to enrolment, eligible patients in study A received monotherapy with an oral antidiabetic agent. Eligible patients in study B were treated with a non-TZD oral antidiabetic therapy for at least 3 months prior to screening, including metformin monotherapy, sulfonylurea monotherapy, or low-dose combination therapy with metformin and sulfonylurea.	Study A N=174 26 weeks Study B N=391 24 weeks	Primary: Mean change in A1C from baseline to the end of treatment Secondary: Proportion of patients with A1C <7% and/or A1C reduction of ≥0.7% at the end of the treatment period, and mean change in FPG	Study A Primary: At week 26, the mean change in A1C from baseline was -0.63% in the RSG 4 mg + GLIM (P=0.03 vs GLIM alone), -1.17% in the RSG 8 mg + GLIM groups (P<0.0001 vs GLIM alone), and -0.08% in the GLIM alone group. Secondary: The mean change in FPG from baseline was -21 mg/dl in the RSG 4 mg + GLIM (P=0.09 vs GLIM alone), -43 mg/dl in the RSG 8 mg + GLIM groups (P<0.0001 vs GLIM alone), and -2 mg/dl for GLIM alone. At week 26, 43% of patients achieved A1C <7.0% in the RSG 4 mg + GLIM group (P=0.0129 vs GLIM alone) and 68% achieved the same A1C goal in the RSG 8 mg + GLIM group (P=0.0001 vs GLIM alone) compared to 32% in the GLIM alone group. Study B Primary: At week 24, the mean change in A1C from baseline was -0.68% in the RSG add-on group compared to -0.08% in the rated GLIM group (P<0.0001). Secondary: The mean change in FPG from baseline was -28 mg/dl in the RSG add-on group compared to -1 mg/dl in the GLIM group (P<0.0001). At week 24, 39% of patients achieved A1C <7% in the RSG add-on group compared to 15% in the GLIM group (P<0.0001). Insulin sensitivity increased significantly in the RSG add-on group but was unchanged with GLIM. β-cell function increased over 24 weeks in both treatment groups but with a significantly greater increase with RSG add-on. RSG add-on significantly reduced fasting levels of C-peptide (P=0.025), proinsulin (P=0.0006) and insulin (P=0.013) and reduced the proinsulin:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				insulin ratio (P<0.0001). There were no significant changes in any of these parameters with GLIM (C-peptide: P=0.075; proinsulin: P=0.42; insulin: P=0.10 and proinsulin: insulin ratio: P=0.34).
Chou et al.[56] (2008) Rosiglitazone/ glimepiride FDC 4 mg/1 mg titrated to 4 mg/4 mg (regimen A) or titrated to 8 mg/4 mg QD (regimen B) (RSG/GLIM) vs rosiglitazone 4 mg titrated to 8 mg QD (RSG) vs glimepiride 1mg titrated to 4 mg QD (GLIM)	RCT, DB, PG Patients 18 to 75 years of age with type 2 diabetes, A1C 7.5% to 12.0%, fasting C-peptide ≥0.8 ng/ml, FPG ≥126 mg/dl line, and who had been treated with diet and/or exercise alone or who had not taken oral antidiabetic medication or insulin for >15 days in the preceding 4 months	N=901 28 weeks	Primary: Change from baseline in A1C after 28 weeks of treatment Secondary: Change in FPG from baseline to week 28, proportion of subjects achieving target A1C (<6.5% or <7%), change from baseline to week 28 in fasting insulin, insulin sensitivity, β-cell function, cardiovascular biomarkers	Primary: At week 28, change in A1C from baseline was -1.7% for GLIM, -1.8% for RSG, -2.4% for RSG/GLIM (regimen A; P<0.0001 vs. both GLIM and RSG) and -2.5% for RSG/GLIM (regimen B; P<0.0001 vs. both GLIM and RSG). Secondary: At week 28, mean change in FPG from baseline was -42.2 mg/dl for GLIM, -56.6 mg/dl for RSG, -69.5 mg/dl for RSG/GLIM (regimen A; P<0.0001 vs. both GLIM and RSG), and -79.9 mg/dl RSG/GLIM (regimen B; P<0.0001 vs. both GLIM and RSG). At week 28, 75% of patients treated with RSG/GLIM (regimen A) and 72% of patients treated with RSG/GLIM (regimen B) achieved A1C <7% compared with RSG (46%, both P<0.0001) or GLIM (49%, both P<0.0001). At week 28, 56% of patients treated with RSG/GLIM (regimen A) and 54% of patients treated with RSG/GLIM (regimen B) achieved A1C <6.5% compared with RSG (31%, both P<0.0001) or GLIM (32%, both P<0.0001). Estimates of insulin sensitivity (HOMA-S) at 28 weeks increased from baseline with all RSG-containing regimens (36.3%, 21.9% and 23.0% for RSG and FDC regimens A and B, respectively) but HOMA-S was not significantly changed with GLIM (-3.2%; P<0.05 vs. both GLIM and RSG). Estimates of β-cell function (by HOMA-B) increased in all groups, but significantly greater improvements were seen in the RSG/GLIM arms (regimen A, 73.4%; regimen B, 105.8%) compared with GLIM (58.7%) or RSG (46.1%; P<0.05 vs. both GLIM and RSG). At 28 weeks, fasting insulin levels were significantly increased in the

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				GLIM arm (20.4% increase from baseline) compared with the RSG/GLIM groups (regimen A, -10.9 pmol/l; regimen B, -7.8 pmol/l), while decreases from baseline were significantly greater in the RSG group compared with RSG/GLIM regimen A or regimen B (-28.7 pmol/l change from baseline). Adiponectin increased from baseline in all RSG-containing treatment groups (RSG, 128.5%; RSG/GLIM regimen A, 65.6%; RSG/GLIM regimen B, 116.5%) in contrast to the GLIM arm, where there was little change (-5.3%). There were significantly greater reductions in CRP from baseline in the RSG/GLIM groups compared with GLIM alone (-43.6% with RSG/GLIM regimen A, -50.7% RSG/GLIM regimen B vs. -7.9% GLIM). A decrease similar to that for the FDC regimens was observed in the RSG arm (-39.8%). Both RSG/GLIM regimens were well tolerated, with safety and tolerability profiles similar to those expected from the component monotherapies. Approximately 50% of subjects in all groups reported at least one on-therapy adverse event (AE). The AE profile was similar across groups. The AEs most frequently reported were headache (4.4%) and nasopharyngitis (4.4%). Overall, 19.5% of subjects reported a hypoglycemic episode while receiving study medication. Fewer subjects receiving RSG reported hypoglycemia (5.2%) than patients receiving GLIM alone (21.6%) or a GLIM-containing regimen (29.0% in RSG/GLIM regimen A and 22.5% in RSG/GLIM regimen B). The median increases in weight from baseline were GLIM 1.10 kg, RSG 1.00 kg, RSG/GLIM regimen A 2.00 kg, and RSG/GLIM regimen B 3.40 kg.
Home et al.[42] (2007) Rosiglitazone plus either metformin or a sulfonylurea vs	MC, OL, PG, RCT (RECORD) Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin	N=1,122 18 months	Primary: Change in A1C from baseline Secondary: Effect on FPG, serum lipids, HOMA basal insulin sensitivity	Primary: At 18 months, A1C reduction on background metformin was similar with rosiglitazone and sulfonylurea (difference 0.07%; 95% CI, –0.09 to 0.23; P=NS), as was the change when rosiglitazone or metformin was added to sulfonylurea (difference 0.06%; 95% CI, –0.09 to 0.20; P=NS). Secondary: Differences in FPG were not statistically significant at 18 months (rosiglitazone vs sulfonylurea –0.36 mmol/L; P=0.062 and rosiglitazone vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metformin plus a sulfonylurea	or a sulfonylurea monotherapy, and inadequate glycemic control (A1C 7% to 9%)		and islet β-cell function (HOMA %β) by the equation method, body weight, inflammatory/ thrombotic markers, C-reactive protein (CRP)	metformin –0.34 mmol/L; P=0.089). Rosiglitazone increased total cholesterol (P≤0.001) and LDL cholesterol (P=0.000) and reduced nonesterified fatty acids (P=0.000) at 18 months compared with the control groups. An increase in HDL cholesterol and triglycerides was observed with rosiglitazone compared with sulfonylurea (0.08 vs 0.02 mmol/L; P=0.001; 0.40 vs 0.15 mmol/L; P=0.016, respectively), but not with metformin (both P=NS). HOMA-estimated basal insulin sensitivity was substantially increased in the rosiglitazone groups compared with the respective controls (both P<0.001). Both rosiglitazone and sulfonylurea when added to metformin increased HOMA %β, but this increase was greater with the sulfonylurea (P<0.001). Rosiglitazone or metformin added to background sulfonylurea also increased HOMA %β, and to a similar extent (P=NS). Rosiglitazone was associated with a significant increase in body weight compared to metformin (P<0.001) and a sulfonylurea (P=0.003). At 18 months, plasminogen activator inhibitor-1 antigen decreased from baseline with rosiglitazone, with a significant difference compared to sulfonylureas (–5.7% vs 7.0%; P=0.047); rosiglitazone and metformin did not differ (P=NS). In both rosiglitazone groups, there was a significant reduction in CRP compared with a sulfonylurea (P<0.001) and metformin (P=0.001).
Komajda et al.[54] (2008) Rosiglitazone plus either metformin or a sulfonylurea vs metformin plus a sulfonylurea	RCT, MC, OL, (RECORD[69]) Patients 40 to 75 years of age with type 2 diabetes and BMI ≥25 kg/m^2, on maximum tolerated doses of metformin or a sulfonylurea monotherapy, and	N=668 12 months	Primary: Change from baseline in 24-hour ambulatory blood pressure at 6 months and 12 months	Primary: For patients receiving rosiglitazone and a sulfonylurea, the reduction in 24-hour systolic blood pressure (sBP) was greater at 6 months (-3.8 mmHg) and 12 months (-3.8 mmHg) than with metformin and sulfonylurea therapy (-1.2 mmHg and -1.3 mmHg, respectively; 6 months, P=0.015; 12 months, P=0.031). Reductions in 24-hour diastolic blood pressure (dBP) were greater at 6 months and 12 months for patients receiving rosiglitazone and a sulfonylurea (-3.1 mm Hg and -3.7 mmHg) compared to metformin and sulfonylurea (-0.4 mmHg and -0.6 mmHg; both P<0.001).

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	inadequate glycemic control (A1C 7% to 9%)			At 12 months, the reduction in 24-hour sBP was greater for rosiglitazone and metformin (-4.9 mmHg) than for metformin and sulfonylurea (-2.2 mmHg; P=0.016). At 12 months, the reduction in dBP was greater for rosiglitazone and metformin (-3.8 mmHg) than for metformin and sulfonylurea (-1.7 mmHg; P=0.003). At 6 months, the reductions in sBP and dBP were not significantly different for rosiglitazone and metformin compared to metformin and sulfonylurea (sBP, P=NS; dBP, P=0.049).
Scott et al.[18] (2008) Rosiglitazone 8 mg once daily and metformin (existing therapy) vs sitagliptin 100 mg once daily and metformin (existing therapy) vs metformin (existing therapy) and placebo	RCT, DB, PG Patients 18-75 years of age who were taking metformin monotherapy at a stable dose of ≥1500 mg/day for at least 10 weeks prior to the screening visit and had inadequate glycemic control (A1C 7% to 11%)	N=273 18 weeks	Primary: Change in A1C from baseline to week 18 Secondary: Fasting plasma glucose (FPG), fasting serum insulin, fasting serum proinsulin	Primary: At week 18, the mean change in A1C from baseline was -0.73% for sitagliptin, -0.79% for rosiglitazone, and -0.22% for placebo (P<0.001 for sitagliptin vs. placebo). There was no significant difference between sitagliptin and rosiglitazone. At week 18, the proportion of patients achieving an A1C <7% was 55% in the sitagliptin group (P=0.006), 63% in the rosiglitazone group, and 38% in the placebo group. There was no significant difference between sitagliptin and rosiglitazone. Secondary: At week 18, the mean change in FPG from baseline was -11.7 mg/dl with sitagliptin, -24.5 mg/dl with rosiglitazone, and 6.1 mg/dl with placebo (P<0.001 for sitagliptin vs. placebo). Rosiglitazone lowered fasting serum insulin and proinsulin relative to placebo or sitagliptin, but the change in the proinsulin/insulin ratio was similar across treatments. There was a higher overall incidence of adverse events (AEs) for sitagliptin (39%) and rosiglitazone (44%) compared to placebo (30%). No differences were observed among the sitagliptin, rosiglitazone and placebo groups with respect to the incidence of SAEs and drug-related AEs. Hypoglycemia and gastrointestinal AEs were similar among the treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				groups.
Rigby et al.[86] (2010) Rosiglitazone 4 mg daily (QD or BID) and metformin (existing therapy) vs sitagliptin 100 mg QD and metformin (existing therapy) vs colesevelam 3.75 g daily (QD or BID) and metformin (existing therapy)	OL Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control (A1C 6.5% to 10.0% on a stable regimen of metformin (1,500-2,550 mg daily), with LDL cholesterol ≥60 mg/dl and triglycerides <500 mg/dl	N=169 16 weeks	Primary: Change in A1C from baseline to week 16 Secondary: Change in A1C from baseline to week 8, change in fasting plasma glucose and fasting insulin from baseline to weeks 8 and 16, change in 2-hour postprandial glucose and postprandial insulin after a meal tolerance test, change in lipid parameters, percentage of participants who achieved an A1C reduction >0.7% from baseline, percentage of participants who achieved A1C <7.0%	Primary: At week 16, A1C was reduced from baseline in all treatment groups (LS mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009). Secondary: At week 8, A1C was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109). Fasting plasma glucose was significantly reduced from baseline at week 8 and week 16 in all treatment groups. The 2-hour postprandial glucose levels were significantly reduced from baseline at week 16 in all treatment groups. There was no significant change in fasting insulin or 2-hour postprandial insulin from baseline to week 16 in any treatment group. Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008). LDL cholesterol was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011). Total cholesterol levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL cholesterol levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median triglyceride levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect triglyceride levels. HDL-cholesterol levels did not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				change significantly from baseline with any treatment. At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in A1C of 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved A1C <7.0%. The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity.
Hollander et al.[19] (2009) Thiazolidinedione (existing therapy) and saxagliptin 2.5 mg QD vs thiazolidinedione (existing therapy) and saxagliptin 5 mg QD vs thiazolidinedione (existing therapy) and placebo	RCT, DB, PC, MC Patients 18-77 years of age with type 2 diabetes treated with a stable dose of a thiazolidinedione monotherapy for at least 12 weeks, A1C 7-10.5%, fasting C-peptide concentration ≥0.3 nmol/liter, and a body mass index (BMI) ≤40 kg/m^2	N=565 24 weeks	Primary: Change from baseline to week 24 in A1C Secondary: Changes from baseline to week 24 in FPG, proportion of patients achieving a therapeutic glycemic response (A1C <7.0%) and postprandial glucose (PPG) response	Primary: Adjusted mean change from baseline to week 24 in A1C was -0.66% for saxagliptin 2.5 mg, -0.94% for saxagliptin 5 mg, and -0.30% for placebo. Compared to placebo, there was a reduction in A1C by -0.36% (saxagliptin 2.5 mg; P=0.0007) and -0.63% (saxagliptin 5 mg; P=0.0007) from baseline to week 24. Secondary: Adjusted mean changes in FPG from baseline to week 24 were greater with saxagliptin 2.5 mg (-0.8 mmol/liter; P=0.0053) and saxagliptin 5 mg (-1.0 mmol/liter; P=0.0005) compared to placebo (-0.2 mmol/liter). The proportion of patients who achieved an A1C <7.0% at week 24 was 42.2% and 41.8% for saxagliptin 2.5 and 5 mg, respectively compared to 25.6% for placebo (P=0.0010 and P=0.0013, respectively compared to placebo). Adjusted mean change in PPG AUC from baseline to week 24 was -436 mmol · min/liter and -514 mmol · min/liter for saxagliptin 2.5 mg and 5 mg, respectively compared to placebo (-149 mmol · min/liter; both P<0.0001). The proportion of patients experiencing any adverse event (AE) was 68.0% (all saxagliptin-treated patients) and 66.8% (placebo). AE frequency was higher for saxagliptin 5 mg (74.2%) than saxagliptin 2.5

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg (62.1%). The most commonly reported AEs (occurring in >5% of saxagliptin-treated patients vs. placebo) were upper respiratory tract infection (8.4 vs. 7.1%), peripheral edema (5.5 vs. 4.3%), and headache (5.0 vs. 3.8%). Rash was the most common skin-related AE and was reported in 0.8% of saxagliptin-treated patients and 0.5% of placebo treated patients.
Pinelli et al.[63] (2008) Thiazolidinediones in combination with other antidiabetic agents vs exenatide in combination with other antidiabetic agents	MA Patients with type 2 diabetes receiving combination therapy	N=9,325 (22 trials) ≥24 weeks	Primary: Mean change in A1C from baseline to study end point Secondary: Proportion of patients reaching A1C <7%, mean change from baseline in FPG and body weight, hypoglycemia, and gastrointestinal adverse events	Primary: There were small reductions in the A1C across the studies. The weighted mean differences were –0.80% (95% CI, –1.10 to –0.50) in the TZD studies and –0.60% (95% CI, –1.04 to –0.16) for exenatide trials. When only placebo-controlled studies were analyzed, there were greater reductions in A1C for both TZDs (weighted mean difference –1.14%; 95% CI –1.30 to –0.98) and exenatide (weighted mean difference –0.97%; 95% CI –1.11 to –0.83). When only TZD active-comparator studies were analyzed, there was a significant difference in A1C levels from baseline (weighted mean difference –0.38%; 95% CI –0.75 to – 0.01. There was no difference in A1C reduction between exenatide and insulin comparators in open-label, non-inferiority trials. Secondary: TZD and exenatide-based therapies were associated with odds ratios of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching A1C <7%. FPG concentrations were reduced from baseline with TZD-based regimens (weighted mean difference –29.58 mg/dL; 95% CI, –39.27 to –19.89), but did not reach statistical significance with exenatide (weighted mean difference –8.77 mg/dL; 95% CI, –28.85 to 11.31). Severe hypoglycemia was rare in the 1 exenatide and 4 TZD trials that identified a total of 9 participants experiencing hypoglycemic episodes. In these 5 trials, participants reporting an event were also receiving an insulin secretagogue. The odds ratio for developing nonsevere hypoglycemia with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				TZDs was not significantly different from other treatment arms (OR 1.59; 95% CI 0.76 to 3.32). In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (weighted mean difference 1.51 kg; 95% CI –0.12 to 3.15). Mean change in body weight from baseline was reduced significantly in the exenatide-based regimens (weighted mean difference –2.74 kg; 95% CI, – 4.85 to –0.64). The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. Odds ratios greater than 1 for nausea, vomiting, and diarrhea were observed with exenatide with pooled odds ratios of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI 2.05 to 4.26), respectively. Nausea occurred in 47% of patients treated with exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients who received exenatide and 4% of patients in the comparator arms. Diarrhea occurred in 12% of patients treated with exenatide and 4% in the comparator arms.
Clar et al.[71] (2009) Pioglitazone in combination with any insulin regimen (with or without other oral hypoglycemic agents) vs insulin (with or without other oral hypoglycemic agents)	MA Patients with type 2 diabetes	N=3,092 (8 trials) ≥12 weeks	Primary: A1C, frequency of hypoglycemia, total daily dose of insulin, weight changes, changes in cardiovascular risk factors, and adverse events	Primary: A1C values were significantly lower in the groups taking pioglitazone plus insulin than in the groups taking insulin without pioglitazone (weighted mean difference -0.58%, 95% CI: -0.70 to -0.46; P<0.00001). There were more patients with hypoglycemic episodes in the pioglitazone plus insulin groups than with insulin without pioglitazone; however, this difference was not statistically significant (relative risk 1.27, 95% CI: 0.99 to 1.63, P=0.06). Insulin dose ranged between 42 to 64 U/day or 0.5 to 1 U/kg/day in the pioglitazone groups and between 55 to 70 U/day and 0.7 to 1.2 U/kg/day in the groups taking no pioglitazone. Weight change ranged between +1.4 and +4.4 kg in the pioglitazone plus insulin groups and between -0.04 and +4.9 kg in the insulin only groups. Four studies reported results for serum triglycerides. Only two of the studies demonstrated a significant reduction in the pioglitazone groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(-0.44 to -0.70 mmol/L) compared to insulin only). None of the studies found a difference in total cholesterol between the pioglitazone plus insulin and the insulin without pioglitazone groups. Four studies reported on HDL-cholesterol and all found significantly increased values in the pioglitazone groups (+0.10 mmol/L to +0.18 mmol/L) compared to insulin only. None of the studies found a difference in LDL-cholesterol between the pioglitazone plus insulin and the insulin without pioglitazone groups. Besides weight gain and hypoglycemia, the only adverse event reported as occurring more frequently with pioglitazone was peripheral edema.
Diabetes Prevention Trials				
Gerstein et al.[38] (2006) Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily vs placebo	MC, PRO, RCT (DREAM) Adults≥30 years of age with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease Ramipril was also included in the trial. Only the results on rosiglitazone are reported here.	N=5,269 3 years	Primary: Composite of incident diabetes or death Secondary: Regression to normoglycemia, composite of cardiovascular events, individual components of the cardiovascular composite, renal events, composite cardiorenal outcome, glucose concentrations	Primary: The composite primary outcome was observed in 11.6% of individuals given rosiglitazone and 26.0% of individuals given placebo (HR, 0.40; 95% CI, 0.35 to 0.46; P<0.0001). There was no difference in the number of deaths (HR, 0.91; 95% CI, 0.55 to 1.49; P=0.7). The frequency of diabetes was reported in significantly fewer patients receiving rosiglitazone than placebo (HR, 0.38; 95% CI, 0.33 to 0.44; P<0.0001). Secondary: Normoglycemia was reported in 1,330 (50.5%) of individuals in the rosiglitazone group and 798 (30.3%) of participants in the placebo group (HR, 1.71; 95% CI, 1.57 to 1.87; P<0001). The frequency of composite cardiovascular outcome was similar between rosiglitazone and placebo. The components of the composite were similar between the two groups with the exception of heart failure, which was reported in 14 (0.5%) participants in the rosiglitazone group and 2 (0.1%) in the placebo group (P=0.01). The median fasting plasma glucose concentration was 0.5 mmol/L lower in the rosiglitazone group than in the placebo group (P<0.0001); the 2-hour plasma glucose concentration was 1.6 mmol/L lower with rosiglitazone than placebo (P<0.0001).
Dagenais et al.[66] (2008)	MC, PRO, RCT (DREAM)	N=5,269 3 years	Primary: Composite cardiovascular	Primary: During the 3-year follow-up, 836 participants had a first occurrence of the composite cardiorenal outcome (2.5% cardiovascular composite outcomes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rosiglitazone 4 mg once daily for 2 months, then 8 mg once daily vs placebo	Adults≥30 years of age with impaired fasting glucose and/or impaired glucose tolerance and no previous cardiovascular disease Ramipril was also included in the trial. Only the results on rosiglitazone are reported here.		outcome and composite renal outcome	and 13.6% renal composite outcomes). The composite cardiorenal outcome occurred in 15.0% of participants allocated to rosiglitazone and 16.8% of participants allocated to placebo (HR, 0.87; 95% CI, 0.75 to 1.01; P=0.07). Rosiglitazone did not reduce the overall risk of cardiovascular events, but significantly increased the risk for heart failure (0.5%) compared to placebo (0.1%; 95% CI, 1.60 to 31.0). Rosiglitazone reduced the renal component of the composite outcome by 20% due to a reduction in progression of albuminuria compared to placebo (HR, 0.80; 95% CI, 0.68 to 0.93; P=0.031). The fall in eGFR by ≥30% was not significant (P=0.087).

*Agent not available in the United States
†Estimates approximate values since results were displayed in bar graph and precise values were not reported
‡Synonym for glyburide
Drug regimen abbreviations: BID=twice daily, QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PM=post marketing, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk
Miscellaneous abbreviations: ACS=acute coronary syndrome, ADOPT=A Diabetes Outcomes Progression Trial, BMI=body mass index, CAD=coronary artery disease, CHF=congestive heart failure, CRP=C-reactive protein, DREAM= Diabetes REduction Assessment with ramipril and rosiglitazone Medication, FDC=fixed-dose combination, FFA=free fatty acids, FPG=fasting plasma glucose, FPI=fasting plasma insulin, GI=gastrointestinal, A1C=glycosylated hemoglobin A1c, HDL=high-density lipoprotein, HOMA=homeostasis model assessment, HOMA-B=homeostasis model assessment of β-cell function, HOMA-S=homeostasis model assessment of insulin sensitivity, LDL=low-density lipoprotein, MI=myocardial infarction, NYHA=New York Heart Association, PPG=postprandial glucose, PPI=postprandial insulin, PROactive=PROspective pioglitAzone Clinical Trial In macroVascular Events, RECORD= Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycemia in Diabetes, TC=total cholesterol, TG=triglycerides

Additional Evidence

Dose Simplification
Vanderpoel at al. investigated the adherence rates with the fixed-dose combination of rosiglitazone and metformin compared to monotherapy or concomitant administration of the individual components.[59] Prescription claims for 16,929 type 2 diabetics were analyzed for a 12-month time period. Adherence pre- and post-index was measured by a medication possession ratio, a proxy measurement to determine adherence. Compared to the pre-index period for concomitant administration of the individual components, the fixed-dose combination product had a significant increase in the medication possession ratio (+4.8; P<0.005). There was no significant difference in pill burden, insulin use rate, or non-study oral hyperglycemic agents between the two groups.

Stable Therapy
Berhanu et el. evaluated changes in lipid profiles in 305 patients with type 2 diabetes and dyslipidemia after treatment conversion from rosiglitazone to pioglitazone with continuation of statin and other lipid-lowering therapies.[43] At 17 weeks after treatment conversion from rosiglitazone to pioglitazone, patients had significant reductions in triglycerides (–15.2%; P<0.0001), total cholesterol (–9.0%; P<0.0001), and low-density lipoprotein (LDL) particle concentration (–189 nmol/L; P<0.0001) without significant changes in A1C (0.02%). LDL cholesterol (+2.2%), high-density lipoprotein cholesterol (+1.8%; P<0.05), and LDL particle diameter (+0.23 nm; P<0.0001) increased as well.

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 15. Relative Cost of the Thiazolidinediones

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Pioglitazone	tablet	Actos®	$$$$-$$$$$	N/A
Pioglitazone and glimepiride	tablet	Duetact®	$$$$$	N/A
Pioglitazone and metformin	tablet	Actoplus Met®, Actoplus Met XR®	$$$$-$$$$$	N/A
Rosiglitazone	tablet	Avandia®	$$$$-$$$$$	N/A
Rosiglitazone and glimepiride	tablet	Avandaryl®	$$$$-$$$$$	N/A
Rosiglitazone and metformin	tablet	Avandamet®	$$$$-$$$$$	N/A

N/A=Not available

X. Conclusions

The thiazolidinediones are approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1-9] There are no generic products available; however, metformin and glimepiride are available generically in a separate formulation.

There are several guidelines that provide recommendations on the treatment of type 2 diabetes. According to the ADA/EASD treatment algorithm, metformin is recommended as first-line therapy, followed by the addition of insulin or a sulfonylurea (Tier 1 algorithm).[11] However, the addition of exenatide or pioglitazone to metformin may be considered if hypoglycemia is a concern (rosiglitazone is not recommended). According to the AACE/ACE algorithm, metformin, thiazolidinediones, DPP-4 inhibitors and alpha-glucosidase inhibitors are all appropriate for use as monotherapy in patients with an A1C between 6.5% and 7.5% due to their minimal risk of hypoglycemia.[12] However, the guidelines state that metformin is the cornerstone of therapy due to its safety and efficacy. An incretin mimetic or a DPP-4 inhibitor is the preferred second agent to use in combination with metformin (regardless of the A1C range). The thiazolidinediones may also be considered for dual or triple therapy, but they are positioned lower than incretin mimetics and DPP-4 inhibitors due to the risk of weight gain, fluid retention, congestive heart failure and fractures. For patients with an A1C of 7.6% to 9.0%, the thiazolidinediones are given a higher priority than insulin secretagogues to minimize the risk of hypoglycemia. For patients with an A1C >9.0%, a sulfonylurea is preferred over a thiazolidinedione because of its greater efficacy and more rapid onset of action. Other guidelines recommend the use of a thiazolidinedione as a second-line treatment option.[14,16-17]

A variety of clinical trials have been conducted with the thiazolidinediones. In comparative studies, the use of pioglitazone and rosiglitazone led to similar improvements in glycemic control.[20,33-34,36,64,81] Several studies evaluated the efficacy of thiazolidinediones in dual therapy regimens compared to monotherapy regimens. In these studies, the more aggressive treatment regimens improved glycemic parameters to a greater extent than the less-intensive treatment regimens.[19,46,50,52-53,55,57,67-68,74,83-84] However, in studies that directly compared various dual therapy regimens, there were no differences in efficacy noted.[18,39,42,60-62,70,72,79] The thiazolidinedione fixed-dose combination products have been shown to be improve glycemic control in patients with type 2 diabetes.[47-49,56,65,67] However, there were no randomized studies found in the medical literature that directly compared the efficacy of the fixed-dose combination products to the coadministration of each component as separate formulations.

Both of the thiazolidinediones may cause weight gain and fluid retention, as well as increase the risk for congestive heart failure and fractures.[1-9] The cardiovascular safety of rosiglitazone has been a controversial issue since 2007. The results of two cardiovascular outcomes studies with the thiazolidinediones have been reported (PROactive and RECORD); however, neither study directly compared pioglitazone and rosiglitazone.[44,69] A variety of meta-analyses and observational studies have been conducted by independent investigators to assess the link between the use of thiazolidinediones and cardiovascular events.[24-26,28-32,45,76,78,87] On September 23, 2010, the FDA notified healthcare providers that it will significantly restrict the use of rosiglitazone in response to data that suggested an increased risk of cardiovascular events with the drug.[82] They are requiring that the manufacturer develop a risk evaluation and mitigation strategy (REMS). Under the REMS, rosiglitazone will only be available to new patients if they are unable to achieve glycemic control on other antidiabetic agents and are unable to take pioglitazone. Current users of rosiglitazone will be able to continue taking the drug if they are benefiting from it. According to the FDA, “doctors will have to attest to and document their patients' eligibility; patients will have to review statements describing the cardiovascular safety concerns associated with this drug and acknowledge they understand the risks.” The FDA also halted the TIDE trial, which was further evaluating the cardiovascular effects of rosiglitazone and pioglitazone in patients with type 2 diabetes.[82,85] On September 17, 2010, the FDA also notified healthcare providers that they have begun a safety review of pioglitazone to further evaluate the risk of bladder cancer after receiving preliminary results from an ongoing, 10-year observational study.[88] Five-year data suggests that there is no overall association between pioglitazone exposure and the risk of bladder cancer; however, there was an increased risk in patients with the longest exposure to the drug and in those receiving the highest cumulative dose. The safety review is ongoing and the FDA has not concluded that pioglitazone increases the risk of bladder cancer.[88]

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with the thiazolidinediones or any other antidiabetic drug.[4-9] Since these agents are not recommended as first-line therapy

for the treatment of type 2 diabetes mellitus, the thiazolidinediones should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand pioglitazone-containing products within the class reviewed are comparable to each other and to the generics and OTC products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Rosiglitazone-containing products have a clinical disadvantage compared to the other brands, generics and OTC products in the class (if applicable).

XI. Recommendations

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

Rosiglitazone-containing products should not be placed in preferred status regardless of cost.

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