Angiotensin Modulators: ACE Inhibitors and Renin Inhibitors Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Key: HTN = hypertension, LVD = left ventricular dysfunction, CAD = coronary artery disease, MI = myocardial infarction, CHF = congestive heart failure

Drug	Manufacturer	HTN	CHF	Post-MI	Other Indications
ACE Inhibitors					
benazepril (Lotensin®)[1]	generic	X (Pediatrics age 6-16 yrs)	--	--	--
captopril (Capoten®)[2,3]	generic	X	X	X (in patients with LVD)	Diabetic Nephropathy in type 1 diabetics
enalapril (Vasotec®, Epaned™)[4,5]	generic (tablets), Silvergate (oral solution)	X (Pediatrics age 1 month -16 yrs)	X (or asymptomatic LVD) only tablets	--	--
fosinopril (Monopril)[6,7]	generic	X (Pediatrics age 6-16 yrs)	X	--	--
lisinopril (Prinivil®, Qbrelis™, Zestril®)[8,9,10]	generic (tablets), Silvergate (oral solution)	X (Pediatrics age 6-16 yrs)	X	X (in hemo-dynamically stable patients)	--
moexipril (Univasc®)[11]	generic	X	--	--	--
perindopril (Aceon®)[12]	generic	X	--	--	In stable CAD, reduces risk of cardiovascular mortality and non-fatal MI
quinapril (Accupril®)[13]	generic	X	X	--	--
ramipril (Altace®)[14]	generic (capsules)	X	X (post-MI)	--	Reduction of risk of MI, stroke, and death from cardiovascular causes
trandolapril (Mavik®)[15]	generic	X	X (post-MI)	X (in patients with CHF or LVD)	--
Renin Inhibitor					
aliskiren (Tekturna®)[16]	Novartis	X	--	--	--

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Diuretic Combination Products

Several ACE inhibitors and the renin inhibitor are available in combination with a diuretic for treatment of hypertension. The fixed dose diuretic combinations are not indicated for initial treatment. The combination results in additional blood pressure reduction with minimal changes in adverse effect profile.[17]

Drug	Manufacturer
ACE Inhibitors	
benazepril/HCTZ (Lotensin HCT®)	generic
captopril/HCTZ (Capozide®)	generic
enalapril/HCTZ (Vaseretic®)	generic
fosinopril/HCTZ	generic
lisinopril/HCTZ (Prinzide®, Zestoretic®)	generic
moexipril/HCTZ (Uniretic®)	generic
quinapril/HCTZ (Accuretic®)	generic
Renin Inhibitor	
aliskiren/HCTZ (Tekturna HCT®)	Novartis

OVERVIEW

Hypertension (HTN) affects approximately 34% of adult Americans. From 2007 to 2014, the death rate from heart disease declined 14.9%, but inpatient cardiovascular operations and procedures increased by 28% from 2000 to 2010. Hypertension is an independent risk factor for the development of cardiovascular disease (CVD).[18] The more elevated the blood pressure, the higher the risk of myocardial infarction (MI), stroke, heart failure, and kidney disease.[19] To reduce the risk of cardiovascular (CV) events, the current blood pressure goal is less than 140/90 mm Hg.[20,21] The American Diabetes Association (ADA) suggests that the blood pressure goal for many people with diabetes and hypertension should be < 140 mmHg systolic and < 90 mmHg diastolic, but that lower systolic targets (such as < 130/80 mmHg) may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.[22] For patients with chronic renal disease, the current goal for blood pressure therapy is less than 130/80 mm Hg.[23] For patients with known coronary artery disease (CAD) or CAD equivalent, stable angina, unstable angina (UA)/non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), the target blood pressure is also less than 130/80 mm Hg.[24] Attainment of blood pressure goals results in a reduced risk of CV events.[25] There is inter-patient variability in response to various antihypertensive classes. In the absence of compelling indications, reaching target blood pressure is central in determining CV benefit in patients with hypertension, not the specific agent used.[26,27,28]

Angiotensin Modulators include the angiotensin-converting enzyme (ACE) inhibitors, the renin inhibitor, and the angiotensin II receptor blockers (ARBs). All agents are used in the management of hypertension. This review will focus on the ACE inhibitors and the direct renin inhibitor, aliskiren (Tekturna). In addition to their use in hypertension, ACE inhibitors have been shown to reduce mortality in CHF, delay progression of diabetic nephropathy, and reduce risk of adverse cardiovascular outcomes in high-risk patients.[29,30,31,32]

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In The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), published in 2003, diuretics were recommended as first-line agents with ACE inhibitors as first-line therapy for treatment of essential hypertension when a diuretic cannot be used or when a compelling indication is present.[33] Since the publication of JNC-7 guidelines for the treatment of hypertension, a meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attack, stroke and death in patients taking HCTZ has been published.[34] Based on 14 studies including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium antagonists. Additionally, the meta-analysis concluded that there are no studies or evidence that HCTZ reduces myocardial infarction, stroke, or death.

As a result, the Eighth Report from the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) suggests that ACE inhibitors, ARBs, thiazides, or calcium channel blockers (CCBs) may be used as first-line therapy for patients with hypertension.[35] In African American patients, CCBs and thiazides are recommended first-line. ACE inhibitors or ARBs are recommended in all adults with CKD as initial or add-on antihypertensive therapy, regardless of race or diabetes status.

The Agency for Healthcare Research and Quality (AHRQ) has published a comparative effectiveness report for the ACE inhibitors, ARBs, and aliskiren.[36] The ACE inhibitors and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. It is possible that aliskiren may be more effective than ACE inhibitors (ramipril) but no differences were found in studies when compared to an ARB (losartan). For mortality and major cardiovascular events, there is insufficient evidence to determine if there are any different effects of ACE inhibitors versus ARBs on these serious outcomes. ACEIs have been shown to have a greater risk of cough than ARBs and the direct renin inhibitor.[37,38,39,40]

In 2017, the American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) jointly published guidelines on the pharmacologic treatment of hypertension in adults 60 years and older.[41] They recommend initiating therapy in those with a systolic blood pressure (SBP) persistently > 150 mmHg with a target SBP < 150 mmHg to reduce risk for mortality, stroke and CV events (strong recommendation/high quality of evidence). Furthermore, they suggest considering starting or intensifying drug therapy in those with a history of stroke or transient ischemic attack (TIA) with goal SBP of < 140 mmHg (weak recommendation/moderate quality of evidence) to reduce risk of recurrent stroke. The guidelines also suggest that providers consider initiating or intensifying drug therapy in patients with a high CV risk to achieve SBP < 140 mmHg to reduce risk for stroke or CV event (weak recommendation/low quality of evidence).

According to the 2013 ACC/AHA guidelines for the management of HF, routine combined use of ACE inhibitors and beta blockers are recommended in all patients with reduced ejection fraction heart failure (HF*r*EF), unless there is a contraindication.[42] Drugs with an indication for HF include many ACE inhibitors and some beta blockers. ARBs indicated for HF when a patient is intolerant to an ACE inhibitor include candesartan and valsartan. Diuretics are recommended in patients with HF*r*EF who have evidence of fluid retention, unless there is a contraindication. Aldosterone antagonists (spironolactone [Aldactone®] and eplerenone [Inspra®]) are recommended in HF*r*EF patients with adequate renal function in conjunction with careful monitoring to reduce the risk of hyperkalemia and renal insufficiency. Digoxin can be beneficial in patients with HF*r*EF, unless contraindicated, to decrease hospitalizations for HF. The combination of hydralazine and isosorbide dinitrate is recommended in

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African Americans with HF*r*EF who are persistently symptomatic with the use of an ACE inhibitor and a beta blocker. The ACC/AHA also recommends the use of ARBs in patients unable to tolerate an ACE inhibitor in patients with heart failure following a non-ST-elevated myocardial infarction (NSTEMI) or ST-elevated myocardial infarction (STEMI).[43,44]

The 2016 ACC/AHA/HFSA Focused Update on New Pharmacologic Therapy for Heart Failure, which updates the 2013 ACCF/AHA guideline on the management of HF, recommends an ACE inhibitor, ARB, or angiotensin receptor-neprilysin inhibitor (ARNI) in addition to a beta-blocker, and aldosterone (in select patients) in patients with chronic HF*r*EF (Class I, Level A [ACE inhibitor, ARB] and B-R [ARNI] evidence).[45] Patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or an ARB should be switched to an ARNI to further reduce morbidity and mortality (Class I, Level B-R evidence). An ARNI should not be administered concomitantly or within 36 hours of an ACE inhibitor or in patients with a history of angioedema. These recommendations are primarily based on the results of the PARADIGM-HF trial in which an ARNI (sacubitril/valsartan [Entresto®]) was found to be superior to enalapril in reducing the risks of death and hospitalization for heart failure. [46]

Beneficial effects of ACE inhibitors are demonstrated in diabetic and nondiabetic nephropathies beyond those expected from lowering blood pressure.[47] In type 1 diabetic patients with hypertension, ACE inhibitors delay the progression of nephropathy regardless of the degree of albuminuria. ACE inhibitors and ARBs delay the progression of nephropathy and delay the increase in albuminuria in hypertensive type 2 diabetics with microalbuminuria.[48]

Diabetic nephropathy develops in 25% to 40% of patients over 20 to 25 years after diabetes onset. The prevalence of microalbuminuria ten years after diagnosis of diabetes is 25%.[49] Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the United States and accounts for 40% of all the patients with ESRD entering a dialysis program.[50] Type 1 and 2 diabetics are both at risk for the development of nephropathy and follow the same progression to renal insufficiency and failure.

The first stage of the development of nephropathy is the presence of microalbuminuria. Microalbuminuria in type 2 diabetes mellitus is associated with increased risk of death and cardiovascular mortality.[51,52,53,54] Overt proteinuria and hypertension are associated with an even higher risk of cardiovascular events. Strategies for preventing the progression of renal failure in patients with diabetes mellitus include glycemic control and blood pressure control. ACE inhibitors have been clearly shown to prevent early death in diabetic patients.[55]

The 2017 American Diabetes Association (ADA), the 2017 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), the 2015 AHA/ADA, and the JNC-8 guidelines suggest that all patients with diabetes should receive ACE inhibitors or ARBs for the treatment of hypertension, to reduce the risk of stroke, and to delay the progression of diabetic nephropathy.[56,57,58,59] Prevention of nephropathy progression is associated with reduced healthcare costs and improvement in mortality.

In the setting of acute myocardial infarction (AMI), ACE inhibitors have been shown to reduce mortality rates even in those with normal left ventricular function.[60,61] ACE inhibitors should be started and continued indefinitely in all patients recovering from ST-elevation myocardial infarction (STEMI) or unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI) with left ventricular ejection fraction (LVEF) of 40% or less and for those with hypertension, diabetes, or chronic kidney disease unless otherwise contraindicated. ACE inhibitors are also considered a reasonable option in patients who are at lower risk.

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In AMI, ACE inhibitors reduce 30-day mortality when therapy is initiated within 36 hours of the acute event.[62] Four studies with 98,496 MI patients were analyzed together. Trials using captopril and lisinopril showed approximately 30% mortality reduction if therapy was initiated within 24 hours of MI symptom onset.[63,64]

PHARMACOLOGY

ACE inhibitors affect the renin-angiotensin-aldosterone system (RAAS). ACE inhibitors prevent conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, by competing with angiotensin I for the active site of ACE. Reduction of angiotensin II formation decreases vasoconstriction, decreases aldosterone secretion, and increases plasma renin. Decreased blood pressure and total peripheral resistance, as well as decreased sodium and water retention, result.[65] Hypothesized local activity within the vascular wall may also impact blood pressure.

ACE inhibitors reduce both preload and afterload through arterial and venous dilatation. In CHF, ACE inhibitors decrease total peripheral resistance, pulmonary vascular resistance, pulmonary capillary wedge pressure, and mean arterial and right atrial pressures. Cardiac index, cardiac output, stroke volume, and exercise tolerance are increased in these patients.[66]

Aliskiren (Tekturna) is a renin inhibitor which targets the renin-angiotensin-aldosterone system (RAAS) at the point of activation by inhibiting renin and blocking conversion of angiotensinogen to angiotensin I, thereby decreasing plasma renin activity (PRA).[67]

Hydrochlorothiazide is a thiazide diuretic that exhibits its pharmacological effects by blocking the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume.[68] Consequently, there are increases in plasma renin activity, aldosterone secretion, and potassium excretion. Co-administration of a thiazide diuretic with an agent that blocks the production or function of angiotensin II may help to decrease potassium loss that occurs with thiazide diuretic therapy. The mechanism of action of the antihypertensive effect of thiazides is unknown.

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PHARMACOKINETICS

Drug	Absorption (%)	Half-Life (hr)	Metabolism	Elimination (%)
ACE Inhibitors				
benazepril (Lotensin)[69]	37	10-11	Yes - to active benazeprilat	Renal: 88 Biliary: 11-12
captopril (Capoten)[70,71]	75	< 3	Yes	Renal: > 95
enalapril (Vasotec, Epaned)[72,73]	60	11	Yes - to active enalaprilat	Renal: 60-78 Hepatic: 33
fosinopril (Monopril)[74]	36	11.5 in HTN 14 in CHF	Yes - to active fosinoprilat	Renal: 44-50 Hepatic: 46-50
lisinopril (Prinivil, Qbrelis, Zestril)[75,76,77]	25 (varies between 6-60)	12	None	Renal: 100
moexipril (Univasc)[78]	13	2-9	Yes - to active moexiprilat	Renal: 13 Feces: 53
perindopril (Aceon)[79]	75	0.8-1	Yes - to active perindoprilat	Renal: 100
quinapril (Accupril)[80]	60	3	Yes - to active quinaprilat	Renal: 61 Hepatic: 37
ramipril (Altace)[81]	50-60	13-17	Yes - to active ramiprilat	Renal: 60 Feces: 40
trandolapril (Mavik)[82]	80	22.5	Yes - to active trandolaprilat	Renal: 33 Hepatic: 66
Renin Inhibitor				
aliskiren (Tekturna)[83]	2.5	24	None	Renal: 25
Diuretic				
HCTZ[84]	50-80	5-15	None	Renal: ≥ 61

Fosinopril does not require dosage adjustment in patients with renal failure.

Captopril has a sulfhydryl group which may contribute to additional side effects such as rash. The absorption of captopril decreases by 30 to 40% if given with food.

Lisinopril and captopril are active drugs. All other ACE inhibitors are prodrugs which require metabolism to active drugs.

Differences among agents with regard to structure and tissue specificity have been identified, but clinical relevance of the differences is not clear.[85] Benazepril, quinapril, and ramipril have the highest tissue specificity. The clinical significance of this finding has yet to be determined.

Aliskiren (Tekturna) AUC and C_{max} are decreased by 71 and 85%, respectively, when administered with a high fat meal. In clinical trials, aliskiren was administered without regard to meals. Patients should take aliskiren at the same time each day.

ACE inhibitor active metabolites tend to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, plasma concentrations tend to be higher. Thus care should be taken in dose selection with use of low initial doses and slow titration. In addition, it may be useful to monitor renal function, especially as it may be further compromised in patients with hypertension, congestive heart failure, or myocardial infarction.

ACE inhibitor and aliskiren (Tekturna) exposure (measured by AUC) is increased in elderly patients.[86,87,88,89,90,91,92,93]

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CONTRAINDICATIONS/WARNINGS[94,95,96,97,98,99,100,101,102,103,104,105,106,107,108]

Aliskiren and aliskiren containing products are contraindicated with angiotensin II receptor blockers (ARBs), or angiotensin converting enzyme inhibitors (ACEIs), in patients with diabetes due to increased risk of renal impairment, hyperkalemia, and hypotension.

Angioedema of the head and neck can occur with any angiotensin modulating agent. Previous angioedema is a contraindication to use of any ACE inhibitor. The renin inhibitor should be avoided in patients with prior angioedema. If angioedema involves the tongue or airway, respiratory distress may occur and could result in death without prompt treatment.

Hypersensitivity to any component of the formulations for ACE inhibitors and renin inhibitors is a contraindication to use. ACE inhibitors should not be used in bilateral renal artery stenosis. No data are available on the use of aliskiren (Tekturna) in patients with unilateral or bilateral renal artery stenosis.

All product labeling for agents in this review contain boxed warning regarding the use of drugs that act directly on the renin-angiotensin-aldosterone system during pregnancy can cause fetal and neonatal morbidity and death and when pregnancy is detected, should be discontinued as soon as possible.

Concomitant use of aliskiren with an ARB or ACEI is not recommended in patients with GFR <60 mL/min.

Caution should be used or these agents should be avoided in patients with hyperkalemia or drugs that increase potassium levels. Caution should be exercised when using aliskiren in patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients including patients on high doses of diuretics, as symptomatic hypotension may occur with initiation of treatment with aliskiren.

Serum potassium should be monitored periodically in patients receiving aliskiren as drugs that affect the renin-angiotensin system can cause hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes, combination use with ARBs or ACEI, non-steroidal anti-inflammatory drug (NSAID) or potassium supplements or potassium sparing diuretics.

Renal function should be monitored periodically in patients treated with aliskiren. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or patients receiving ARB, ACEI or NSAID therapy may be at particular risk for developing acute renal failure on aliskiren. In patients who develop a clinically significant decrease in renal function, withholding or discontinuing therapy should be considered.

Hypersensitivity and angioedema requiring airway management and hospitalization have occurred with aliskiren as well as peripheral edema, and severe cutaneous adverse reactions (e.g., Stevens Johnson syndrome and toxic epidermal necrolysis).

Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms such as acute onset of decreased visual acuity or ocular pain can occur within hours to weeks of drug initiation. If untreated, acute angle-closure glaucoma can lead to permanent vision loss. Hydrochlorothiazide should be discontinued as rapidly as possible. Prompt medical or surgical treatments may be considered if the intraocular pressure remains uncontrolled.

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Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

DRUG INTERACTIONS[109,110,111,112,113,114,115,116,117,118,119,120,121,122]

ACE inhibitors can potentially interact with the following agents: azathioprine, cyclosporine, lithium, NSAIDs including selective COX-2 inhibitors, potassium-sparing diuretics, trimethoprim, gold therapy, macrolide antibiotics, or eplerenone. Concurrent use of loop and thiazide diuretics can increase the risk of hypovolemia, increasing the risk of nephrotoxicity.

Aliskiren (Tekturna) is metabolized by CYP3A4. P-glycoprotein (Pgp) is the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter. Atorvastatin, cyclosporine, and ketoconazole are potent Pgp inhibitors.

Drug interactions with aliskiren (Tekturna) have occurred with irbesartan (Avapro®) (50% reduction in aliskiren concentrations), atorvastatin (Lipitor®) (50% increase in aliskiren's maximum concentration and area under the curve), ketoconazole (80% increase in aliskiren levels when administered with ketoconazole 200 mg twice daily), and furosemide (reduced furosemide's maximum concentration and area under the curve by 50% and 30%, respectively). Concomitant use of aliskiren with cyclosporine or itraconazole is not recommended. Co-administration of cyclosporine 200 mg and 600 mg, with aliskiren 75 mg has shown an approximate 2.5-fold increase in maximum concentration and five-fold increase in area under the curve of aliskiren. Coadministration of 240 mg of verapamil with 300 mg aliskiren resulted in an approximately 2-fold increase in aliskiren exposure. However, no dosage adjustment is necessary.

The effects of aliskiren (Tekturna) on warfarin pharmacokinetics have not been evaluated in a well controlled clinical trial. No significant interactions have been reported with lovastatin, atenolol, warfarin, digoxin, celecoxib (Celebrex®), hydrochlorothiazide, ramipril, valsartan, metformin, or amlodipine.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including Selective COX-2 Inhibitors, with ACE Inhibitors and other drugs that affect the renin-angiotensin system, including aliskiren, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving ACE Inhibitors and NSAID therapy.

Dual blockade of the renin-angiotensin-aldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function and electrolytes in patients on ACEs, ARBs or aliskiren.

The ALTITUDE study, a phase III, double-blind trial evaluated the use of aliskiren in addition to conventional therapy in patients with type 2 diabetes and renal impairment, who are at high risk of cardiovascular and renal events.[123] Patients (n=8,606) were randomized to receive either aliskiren 300 mg or placebo, in addition to conventional therapy, including an ACE inhibitor or ARB. The study was halted early. The Data Monitoring Committee identified a higher incidence of non-fatal stroke, renal complications, hyperkalemia and hypotension after 18-24 months of therapy in the aliskiren arm of the study. The study sponsor, Novartis, recommended that ALTITUDE investigators remove aliskiren-based products from their patients' treatment regimen and review their high blood pressure medication. Novartis is also reviewing the findings of other clinical studies involving aliskiren and combination

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therapies. Novartis recommends healthcare professionals should stop aliskiren-containing medications in diabetic patients who are also taking an ACE inhibitor or an ARB. Alternative antihypertensive therapy should be considered.

ADVERSE EFFECTS

Hypertensive Patients

Drug	Headache	Dizziness	Fatigue	Cough	Rash	Angioedema
ACE Inhibitors						
benazepril (Lotensin)[124] n=964	6.2 (4.2)	3.6 (2.4)	2.4 (2.2)	1.2 (1)	reported	0.5
captopril (Capoten)[125, 126]	0.5-2	0.5-2	0.5-2	reported	4-7	< 1
enalapril (Vasotec, Epaned)[127, 128] n=2,314	5.2 (9.1)	4.3 (4.3)	3.0 (2.6)	1.3 (0.9)	1.4 (0.4)	0.2
fosinopril[129] n=688	> 1 (> 1)	1.6 (0)	> 1 (> 1)	2.2 (0)	0.2-1 (reported)	0.2-1
lisinopril (Prinivil, Qbrelis, Zestril)[130,131,132] n=1,349	5.7 (1.9)	5.4 (1.9)	2.5 (1)	3.5 (1)	1.3 (0.5)	0.1
moexipril (Univasc)[133] n=674	> 1 (> 1)	4.3 (2.2)	2.4 (1.8)	6.1 (2.2)	1.6 (0.9)	< 0.5
perindopril (Aceon)[134] n=789	nr	8.2 (8.5)	nr	12 (4.5)	reported	0.1
quinapril (Accupril)[135] n=1,563	5.6 (10.9)	3.9 (2.6)	2.6 (1)	2 (0)	1.4 (1)	0.1
ramipril (Altace)[136] n=651	5.4	2.2	2 (1)	12	< 1	0.3
trandolapril (Mavik)[137] n=832	> 1 (> 1)	1.3 (0.4)	> 1 (> 1)	1.9 (0.4)	0.3-1	0.13
Renin Inhibitor						
aliskiren (Tekturna)[138]	> 1 (>1)	> 1 (>1)	> 1 (>1)	1.1* (0.6)	1 (0.3)	0.06-0.4

nr = not reported

Adverse effects are reported as a percentage. Adverse effects data obtained are from the prescribing information and are not meant to be comparative or all inclusive. Placebo incidences, when available, are indicated in parentheses. *Rates are one-third to one-half of active-controlled trials with ramipril and lisinopril.

The most commonly reported adverse event with aliskiren (Tekturna) 300 mg was diarrhea at 2.3%.

Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials.

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SPECIAL POPULATIONS[139,140,141,142,143,144,145,146,147,148,149,150,151]

Pediatrics

Several ACE inhibitors including benazepril, enalapril, fosinopril, and lisinopril have been shown to be safe and effective in children ages six to 16 years. Enalapril can be used in children as young as one month old.

Ramipril (Altace) was studied in 352 pediatric patients with elevated or high normal blood pressure and chronic renal failure and found effective in reducing blood pressure and proteinuria. Ramipril (Altace) is not FDA-approved for use in children.[152]

Aliskiren (Tekturna) has not been studied in patients less than 18 years of age.[153]

Geriatrics

No overall differences in safety or effectiveness are noted between elderly and younger patients for agents in this class

Pregnancy

All ACE inhibitors and aliskiren (Tekturna) are Pregnancy Category D.[154,155,156,157] All products carry a boxed warning for fetal toxicity. When pregnancy is detected, discontinue medication as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. Avoid use in pregnancy.

Other populations

African American patients receiving ACE inhibitor monotherapy have reported a higher incidence of angioedema compared to non-African Americans. In controlled clinical trials, ACE inhibitors have less effect on blood pressure in African American patients than in non-African Americans.[158,159,160]

Patients with severe renal impairment were excluded from clinical trials of aliskiren (Tekturna) in hypertension.[161] Therefore, caution should be exercised in this population due to the lack of safety data with aliskiren in these patients and the potential renal effects (e.g., increase serum creatinine and blood urea nitrogen) of other agents which act on the renin-angiotensin system.

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DOSAGES

Drug	Hypertension (Adult)	Hypertension (Pediatric)	CHF	Post-MI	Diabetic Nephropathy	Reduce risk of CV outcomes	Stable CAD – reduce CV mortality/ nonfatal MI	Availability
ACE Inhibitors								
benazepril (Lotensin)[162]	10-40 mg daily	0.2-0.6 mg/kg/day; doses > 0.6 mg/kg or > 40 mg have not been studied	--	--	--	--	--	5, 10, 20, 40 mg tablets
captopril (Capoten)[163, 164]	12.5-150 mg three times daily	--	6.25-150 mg three times daily	6.25-50 mg three times daily	25 mg three times daily	--	--	12.5, 25, 50, 100 mg tablets
enalapril (Vasotec, Epaned)[165, 166]	5-40 mg daily	0.08 mg/kg/day up to 5 mg daily; doses > 0.58 mg/kg or > 40 mg have not been studied	2.5-20 mg twice daily (only tablets)	--	--	--	--	2.5, 5, 10, 20 mg tablets Epaned: 1 mg/mL oral solution; 1 mg/mL powder for solution kit with diluent
fosinopril[167]	10-40 mg daily	For children > 50 kg, 5-10 mg daily	10-40 mg daily	--	--	--	--	10, 20, 40 mg tablets
lisinopril (Prinivil, Qbrelis, Zestril)[168,169,170]	10-40 mg daily	0.07 mg/kg/day up to 5 mg; doses > 0.61mg/kg or > 40 mg have not been studied	5-40 mg daily	5-10 mg daily	--	--	--	2.5, 5, 10, 20, 30, 40 mg tablets Qbrelis: 1 mg/mL oral solution
moexipril (Univasc)[171]	7.5-30 mg daily	--	--	--	--	--	--	7.5, 15 mg tablets
perindopril (Aceon)[172]	4-16 mg daily	--	--	--	--	--	4-8 mg daily	2, 4, 8 mg tablets
quinapril (Accupril)[173]	10-80 mg daily	--	5-20 mg twice daily	--	--	--	--	5, 10, 20, 40 mg tablets
ramipril (Altace)[174]	2.5-20 mg daily	--	2.5-5 mg twice daily	--	--	2.5-10 mg daily	--	1.25, 2.5, 5, 10 mg capsules

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Dosages (continued)

Drug	Hypertension (Adult)	Hypertension (Pediatric)	CHF	Post-MI	Diabetic Nephropathy	Reduce risk of CV outcomes	Stable CAD – reduce CV mortality/ nonfatal MI	Availability
ACE Inhibitors *(continued)*								
trandolapril (Mavik)[175]	1-4 mg daily	--	1-4 mg daily	1-4 mg daily	--	--	--	1, 2, 4 mg tablets
Renin Inhibitor								
aliskiren (Tekturna)[176]	150-300 mg daily	--	--	--	--	--	--	150, 300 mg tablets

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Combinations with Hydrochlorothiazide (HCTZ)

Patients' blood pressure not adequately controlled with an ACE inhibitor or HCTZ monotherapy may require combination therapy. Dosage must be guided by clinical response.

In patients with severe renal impairment (creatinine clearance is < 30 mL/min, serum creatinine >3 mg/dL), loop diuretics are preferred to thiazides, so combinations with HCTZ are not recommended.

Drug	Availability
ACE Inhibitors/HCTZ	
benazepril/HCTZ (Lotensin HCT)	5/6.25, 10/12.5, 20/12.5, 20/25 mg/mg tablets
captopril/HCTZ (Capozide)	25/15, 25/25, 50/15, 50/25 mg/mg tablets
enalapril/HCTZ (Vaseretic)	5/12.5, 10/25 mg/mg tablets
fosinopril/HCTZ	10/12.5, 20/12.5 mg/mg tablets
lisinopril/HCTZ (Prinzide, Zestoretic)	10/12.5, 20/12.5, 20/25 mg/mg tablets
moexipril/HCTZ (Uniretic)	7.5/12.5, 15/12.5, 15/25 mg/mg tablets
quinapril/HCTZ (Accuretic)	10/12.5, 20/12.5, 20/25 mg/mg tablets
Renin Inhibitor/HCTZ	
aliskiren/HCTZ (Tekturna HCT)	150/12.5, 150/25, 300/12.5, 300/25 mg/mg tablets

DOSAGE CONSIDERATIONS

ACE Inhibitors

benazepril (Lotensin) – For patients with creatinine clearance < 30 mL/min/1.73 m^2 (serum creatinine >3 mg/dL), the recommended initial dose is benazepril 5 mg once daily.[177]

captopril (Capoten) – For patients with creatinine clearance 10-50 mL/min/1.73 m^2, the initial dose should be reduced by 25%. For patients with creatinine clearance less than 10 mL/min/1.73 m^2, the dose should be reduced by 50%.[178]

enalapril (Vasotec, Epaned) – For hypertensive patients with creatinine clearance < 30 mL/min (serum creatinine >3 mg/dL), the initial dose is 2.5 mg once daily. In patients with heart failure and renal impairment or hyponatremia, enalapril should be initiated at 2.5 mg once daily. Therapy may be increased to enalapril 2.5 mg twice daily, then 5 mg twice daily and higher as needed.[179,180]

fosinopril (Monopril) – No dosage adjustments are necessary for renal impairment.[181]

lisinopril (Prinivil, Qbrelis, Zestril) – For patients with renal impairment (serum creatinine >3 mg/dL or estimated creatinine clearance < 30 mL/minute) and heart failure or hyponatremia (serum sodium < 130 mEq/L), lisinopril therapy should be initiated at 2.5 mg once daily. For hypertensive patients with renal impairment, the initial lisinopril dose is 5 mg once daily. For patients on hemodialysis, the initial dose of lisinopril is 2.5 mg once daily.[182, 183,184] A 200 mL (1 mg/mL) oral suspension may be made using ten 20-mg tablets of lisinopril; see prescribing information for details. [185]

moexipril (Univasc) – For patients with creatinine clearance < 40 mL/min/1.73 m^2, an initial dose of moexipril 3.75 mg once daily should be given cautiously.[186]

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perindopril (Aceon) – In patients with renal impairment (creatinine clearance < 30 mL/min), safety and efficacy of perindopril have not been established. For patients with mild to moderate renal impairment, the dose should be in a range of 2 to 8 mg/day.[187, 188]

quinapril (Accupril) – The recommended initial dose of quinapril is 2.5 mg in patients with a creatinine clearance of 10 to 30 mL/min. There are insufficient data for dosage recommendation in patients with a creatinine clearance less than 10 mL/min.[189]

ramipril (Altace) – In patients with creatinine clearance < 40 mL/min/1.73 m^2 (serum creatinine approximately >2.5 mg/dL) or patients with hypertension and renal impairment, the recommended initial dose is ramipril 1.25 mg once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. For patients with heart failure and renal impairment, the recommended initial dose is ramipril 1.25 mg once daily. The dose may be increased to 1.25 mg twice daily, up to a maximum dose of 2.5 mg twice daily.[190]

trandolapril (Mavik) – For patients with renal impairment (estimated creatinine clearance < 30 mL/min) or hepatic cirrhosis, the initial daily dose is trandolapril 0.5 mg. Dosage may be titrated for optimal response.[191]

Renin Inhibitor

aliskiren (Tekturna) – Aliskiren has not been studied in patients with impaired renal function defined as serum creatinine greater than 1.7 mg/dL for women and greater than 2 mg/dL for men and/or estimated creatinine clearance < 30 mL/minute.[192] No initial dosage adjustment is required in elderly patients, patients with mild to severe renal impairment, or patients with mild to severe hepatic insufficiency. Patients should establish a routine pattern for taking aliskiren with regard to meals. High fat meals decrease aliskiren absorption substantially.[193]

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled trials comparing agents within this class within the last five years for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

The literature review of significant trials comparing agents within this therapeutic class is complete as of February 27, 2017.

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ACE Inhibitors

Numerous clinical trials utilizing ACE inhibitors were published in the 1980's and 1990's. Little evidence suggests one drug is better than others for the approved indications. Many of the ACE inhibitors have been compared in short-term trials evaluating antihypertensive effects. Experience from comparative trials suggests there are few differences among the ACE inhibitors in antihypertensive efficacy when equipotent doses of each agent are used.[194]

Leonetti and colleagues reviewed ACE inhibitors to determine which agent should be used for specific patients.[195] The authors found no significant difference in antihypertensive efficacy or adverse effect profiles among agents. Clinically, the pharmacokinetic differences do not appear to affect the choice of agent.

Garg and colleagues reviewed randomized trials of ACE inhibitor therapy in patients with heart failure.[196] The authors found 32 trials (n=7,105) which met inclusion criteria. The agents studied included captopril, enalapril, ramipril, quinapril, and lisinopril. The two largest trials used enalapril, and the primary endpoint was mortality. Five smaller trials used captopril and evaluated mortality and/or morbidity as the outcome parameter. A statistically significant reduction in mortality for patients on ACE inhibitors versus controls was demonstrated in all trials. The largest amount of data is from trials using enalapril. A separate analysis excluding the SOLVD trial showed a significant reduction in progressive heart failure mortality.[197] The authors concluded the overall mortality results were consistent with those of two major trials, SOLVD and CONSENSUS.[198] An extension of the SOLVD trial demonstrated enalapril used for three to four years extended median survival by 9.4 months.[199]

Numerous studies cite underutilization of ACE inhibitors in the treatment of CHF and acute MI.[200, 201, 202, 203] Elderly patients are most affected by underdosing and underutilization. Achievement of target doses and appropriate patient selection may improve outcomes. The ATLAS study with lisinopril demonstrated patients achieving high doses had a 12% lower risk of death or hospitalization for any reason (p=0.002) and 24% fewer hospitalizations for heart failure (p=0.002) compared to the low dose group.[204] In patients with severe heart failure, the use of high-dose lisinopril, beta-blocker, and digoxin therapy had 12% lower risk of death and hospitalization over one year than patients who received low-dose lisinopril only (p=0.006).[205]

In the OPTIMAAL trial, losartan (Cozaar) and captopril displayed similar effects on morbidity and mortality in 5,477 patients with heart failure or left ventricular dysfunction (LVD) following an acute MI.[206] Captopril and losartan improved systolic and overall LVD function, but greater benefit was observed with captopril.[207]

In patients with LVD after acute MI, trandolapril therapy decreased mortality, decreased sudden death, and reduced the risk of development of severe heart failure. However, in a small study, trandolapril did not improve exercise tolerance or NYHA functional class.[208, 209]

The HOPE trial with ramipril (Altace) demonstrated a reduction in death, MI, and stroke in patients with vascular disease or diabetes and other cardiovascular risk factors.[210] Ramipril reduced the rate of development of new onset heart failure by 24% in high-risk patients with ejection fractions >40% (preserved left ventricular function).[211] Further beneficial effects from the HOPE study were observed in the post-follow-up period of 2.6 years. Patients on ramipril experienced a reduction in relative risk of MI and revascularization, as well as a reduced risk of new onset diabetes.[212] In another study, low-dose ramipril 1.25 mg daily had no effect on cardiovascular and renal outcomes of patients with type 2

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diabetes and albuminuria, despite a slight decrease in blood pressure and urinary albumin concentration.[213] Ramipril (Altace) reduced mortality in patients with heart failure following acute MI.[214]

The DREAM trial was a randomized, double-blind, three-year study of 5,269 patients with impaired fasting glucose levels or impaired glucose tolerance but without cardiovascular disease.[215] The primary outcome was the occurrence of newly diagnosed diabetes or death. Secondary outcomes included composite of cardiac and renal events, glucose levels, and regression to normal glucose levels. Patients received ramipril (Altace) up to 15 mg per day or matching placebo [and rosiglitazone (Avandia®) or matching placebo]. The ramipril (18.1%) group did not differ from the placebo (19.5%) group for the primary outcome, the rate of death or diabetes (hazard ratio=0.91; 95% CI, 0.81 to 1.03; p=0.15). The ramipril group was more likely to have regression to normoglycemia compared to placebo (hazard ratio=1.16; 95% CI, 1.07 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 (102.7 mg/dL) than in the placebo group (103.4 mg/dL, p=0.07), though plasma glucose levels two hours after an oral glucose load were significantly lower in the ramipril group (135.1 mg/dL versus 140.5 mg/dL, p=0.01). Treatment with rosiglitazone significantly reduced the incidence of diabetes or death (hazard ratio=0.4; 95% CI, 0.35 to 0.46, p<0.001). There were no significant interactions, indicating that the effect of ramipril was the same in the presence or absence of rosiglitazone with respect to the primary outcome, secondary outcomes, or their components (p>0.11 for all interactions). The results for the regression to normoglycemia were similar. Although ramipril did not significantly prevent diabetes in this patient population, it did show regression to normal glucose levels. In addition, compared to placebo, neither ramipril nor rosiglitazone reduced the risk of the cardiorenal composite outcome.[216] Ramipril had no impact on the CVD and renal components.

The PROGRESS trial showed the combination of perindopril (Aceon) and indapamide (Lozol®) reduced the risk of stroke among patients with history of stroke or transient ischemic attack (TIA) regardless of the presence or absence of hypertension.[217] Monotherapy with perindopril produced no significant reduction in the risk of stroke. In the EUROPA study, which included 13,655 stable CAD patients without evidence of CHF, perindopril demonstrated a relative risk reduction of 20% for the composite of cardiovascular mortality, MI, or cardiac arrest over the mean study period of more than four years.[218] Benefits were seen with perindopril in stable CAD patients without CHF despite concurrent use of lipid lowering therapy, antiplatelet therapy, and beta-blockers in a majority of patients. The diabetic population with CAD (n=1,502) in the EUROPA trial was evaluated separately in the PERSUADE trial to assess the effect of perindopril on the cardiovascular composite endpoint of cardiovascular death, non-fatal MI, and resuscitated cardiac arrest.[219] Over a median of 4.3 years, the composite outcome was reported in 12.6 versus 15.5% for perindopril and placebo groups, respectively (relative risk reduction, 19% [(95% CI, -7 to 38%), p=0.13].

In the PREAMI study, perindopril (Aceon) 8 mg daily reduced the combined primary endpoint of death, hospitalization for heart failure, and left ventricular remodeling compared to placebo over a 12-month period.[220] In the double-blind, randomized trial, 1,252 patients aged 65 years or older with a LVEF of 40% or higher and a recent history of MI were enrolled. The primary endpoint reached statistical significance and occurred in 35% and 57% of the perindopril and placebo groups, respectively (absolute risk reduction 0.22; 95% CI, 0.16 to 0.28; p<0.001). Fewer patients on perindopril experienced remodeling defined as ≥ 8% increase in LV end diastolic volume as measured by echocardiography (28

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versus 51% with placebo, absolute risk reduction 0.23; 95% CI, 17 to 30; p<0.001). No differences between groups were noted in the number of deaths or hospitalizations.

In the PEACE trial, 8,290 patients with CAD with normal or slightly reduced left ventricular function were randomized to trandolapril 4 mg daily or placebo in addition to intensive conventional therapy.[221] Patients (mean age 64 years) had a mean blood pressure of 133/78 mm Hg and mean left ventricular ejection fraction (LVEF) of 58% at baseline. Of those who received intensive therapy, 72% had a history of coronary revascularization, and 70% were on lipid-lowering therapy. The primary endpoint was the composite of cardiovascular death, MI, or coronary revascularization which occurred over a mean of 4.8 years in 21.9 and 22.5% in the trandolapril and placebo groups, respectively (hazard ratio 0.96 for trandolapril; p=0.43).

The INVEST trial compared the combination of verapamil SR and trandolapril with atenolol and hydrochlorothiazide in 22,576 hypertensive CAD patients over 50 years old with dosage titration ranges of 120 to 480 mg/day, 1 to 8 mg/day, 25 to 200 mg/day, and 12.5 to 100 mg/day for verapamil SR, trandolapril, atenolol, and hydrochlorothiazide, respectively.[222] In the randomized, open-label, blinded endpoint, multinational trial, patients were randomized to verapamil SR or atenolol. After a mean follow-up of 2.7 years, the rates of all-cause mortality, nonfatal myocardial infarction (MI), or nonfatal stroke, and BP control and goal attainment were similar in both groups.

A subgroup of patients with CAD from the INVEST trial were evaluated for newly diagnosed diabetes during follow-up.[223] Newly diagnosed diabetes was significantly less frequent in the verapamil SR group versus atenolol group (7% versus 8.2%, HR 0.85, 95% CI, 0.76 to 0.95, p<0.01). Risk factors for newly diagnosed diabetes included US residence, left ventricular hypertrophy, previous stroke/transient ischemic attack, and Hispanic ethnicity. The addition of trandolapril to verapamil SR decreased the risk of new-onset diabetes (2 and 180 mg/day, respectively, HR 0.56, 95% CI, 0.43 to 0.74; 4 and 240 mg/day, respectively, HR 0.58, 95% CI, 0.44 to 0.78) and the addition of hydrochlorothiazide to atenolol increased the risk (12.5 and 50 mg/day, respectively, HR 1.07, 95% CI, 0.84 to 1.35; 25 and 100 mg/day, respectively, HR 1.38, 95% CI, 1.06 to 1.8).

telmisartan (Micardis) and ramipril

ONTARGET was a randomized, double-blind, multicenter study of 25,620 patients with controlled hypertension with vascular disease or high-risk diabetes.[224] After a three week single-blind run-in period, patients were randomized to ramipril 10 mg daily, telmisartan 80 mg daily, or a combination of ramipril 10 mg and telmisartan 80 mg daily. The primary composite endpoint of the 56-month study was death from CV causes, MI, stroke, or hospitalization for HF. The primary outcome occurred in 1,412 patients versus 1,423 patients (16.5% versus 16.7%, RR, 1.01, 95% CI, 0.94 to 1.09), in the ramipril versus telmisartan groups, respectively. The telmisartan group had lower rates of cough (1.1% versus 4.2%, p<0.001) and angioedema (0.1% versus 0.3%, p=0.01) and a higher rate of hypotensive symptoms (2.6% versus 1.7%, p<0.001) compared to ramipril. The rate of syncope was the same in both groups (0.2%). In the combination group, the primary outcome occurred in 1,386 patients (16.3%, RR 0.99, 95% CI, 0.92 to 1.07) and there was an increased risk of hypotensive symptoms (4.8% versus 1.7%, p<0.001), syncope (0.3% versus 0.2%, p=0.03), and renal dysfunction (13.5% versus 10.2%, p<0.001) compared to the ramipril group. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less adverse events. The combination of the two drugs was associated with more adverse events without an increase in benefit.

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A pre-specified analysis of renal outcomes of the ONTARGET study, a 56-month, randomized, double-blind, multicenter study of 25,620 patients with controlled hypertension with vascular disease or high-risk diabetes, showed that a composite primary renal end point of dialysis, doubling of serum creatinine, and death was similar for telmisartan 80 mg versus ramipril 10 mg, 13.4% versus 13.5%, respectively (HR 1, 95% CI, 0.92 to 1.09) but was increased with combination therapy 14.5% (HR 1.09, 95% CI, 1.01 to 1.18, p=0.037).[225] Secondary outcomes of dialysis and doubling of creatinine had similar findings. Estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan (−2·82 [SD 17·2] mL/min/1.73 m^2 versus −4·12 [SD 17·4], p<0·0001) or combination therapy (−6·11 [SD 17·9], p<0·0001). Compared with ramipril, the increase in urinary albumin excretion was less with telmisartan (p=0.004) or with combination therapy (p=0.001). In the study of patients with high vascular risk, telmisartan was similar to ramipril in reducing renal outcomes. However, combination therapy worsened renal outcomes and was associated with increased adverse events.

The effects of the addition of an ACE inhibitor (ramipril) to an ARB (telmisartan) for a mean follow-up of 56 months in people with diabetes (n = 9,628) who participated in the ONTARGET trial, divided by those with (n=3,163) and without (n=6,465) nephropathy were examined by the original investigators.[226] Participants were compared who were receiving monotherapy with either ramipril or telmisartan with those on dual therapy. SBP decreased more with dual-therapy as compared to monotherapy (-7.1 versus -5.3 mmHg; p<0.0001) and the same number of strokes occurred (1.19 versus 1.22 per 100 patient-years; HR 0.99, 95% CI 0.82-1.2). Stroke rate was greater in participants "with" than those "without" diabetic nephropathy (1.5 versus 1.0 per 100 patient-years), but effects of dual-therapy compared to monotherapy were not different in either subgroup (1.59 versus 1.55 and 1.01 versus 1.08 per 100 patient-years; p=0.60). Other CV and renal outcomes examined, such as dialysis or doubling of serum creatinine, showed no difference between dual-therapy and monotherapy in subgroups, but adverse events, namely acute dialysis, hyperkalemia and hypotension, was more frequent with dual therapy.

Renin Inhibitor

aliskiren (Tekturna) with hydrochlorothiazide (HCTZ)

A randomized, double-blind, placebo-controlled, parallel-group, 15-arm factorial study of 2,776 patients on aliskiren 75, 150, and 300 mg and HCTZ 6.25, 12.5, and 25 mg was conducted. Evaluations of each agent alone and in combination were completed in an eight week study.[227] Greater blood pressure reductions were achieved with combination therapy compared with monotherapy.

Aliskiren was studied in obese patients (body mass index ≥ 30 g/m^2) with hypertension.[228] A total of 560 patients received single-blind HCTZ 25 mg for four weeks. Non-responders (n=489) were randomized in a double-blind fashion to HCTZ plus one of the following: aliskiren 150 mg, irbesartan 150 mg, amlodipine 5 mg or placebo for four weeks. Doses of aliskiren, irbesartan, and amlodipine were doubled and given in addition to HCTZ 25 mg daily. After the total of eight weeks, aliskiren/HCTZ decreased BP significantly more than placebo/HCTZ (-15.8/-11.9 mm Hg versus -8.6/-7.9 mm Hg, p<0.0001) and produced similar BP reductions as irbesartan/HCTZ (-15.4/-11.3 mm Hg) and amlodipine/HCTZ (-13.6/-10.3 mm Hg). Tolerability of aliskiren/HCTZ was similar to placebo. The amlodipine/HCTZ arm had the highest incidence of adverse events, with peripheral edema occurring in 11.1% of patients.

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A randomized, double-blind study compared a single-pill combination of once-daily aliskiren and HCTZ (300/25 mg or 300/12.5 mg) or aliskiren 300 mg monotherapy in 880 patients with hypertension and an inadequate BP response to aliskiren monotherapy.[229] At the week eight endpoint, aliskiren/HCTZ 300/25 mg and 300/12.5 mg provided significantly greater least-squares mean changes in mean sitting systolic/diastolic BP (msSBP/DBP) reductions from baseline (15.9/11 mm Hg and 13.5/10.5 mm Hg, respectively) than aliskiren 300 mg alone (8/7.4 mm Hg; both p<0.001). Rates of blood pressure control (<140/90 mm Hg) were significantly higher with aliskiren/HCTZ 300/25 mg (60.2%) and 300/12.5 mg (57.9%) than with aliskiren 300 mg alone (40.9%; both p<0.001). Aliskiren/HCTZ single-pill combination treatment showed similar tolerability to aliskiren monotherapy.

A double-blind, multicenter study randomized 1,124 patients with mean sitting diastolic blood pressure (msDBP) 95 to 109 mm Hg to aliskiren 150 mg, HCTZ 12.5 mg, or placebo once daily.[230] Forced titration to aliskiren 300 mg or HCTZ 25 mg occurred at week three. At week six, patients receiving placebo were reassigned (1:1 ratio) to aliskiren 300 mg or HCTZ 25 mg. From week 12, amlodipine 5 mg was added and titrated to 10 mg from week 18 for patients who's BP remained uncontrolled. BP reductions (msSBP/DBP) were significantly greater with aliskiren compared to HCTZ based treatment at week 26 (-20.3/-14.2 versus -18.6/-13 mm Hg; p<0.05) and were also greater at week 52 (-22.1/-16 versus -21.2/-15 mm Hg; p<0.05 for mean msDBP). At the end of the monotherapy period (week 12), aliskiren 300 mg was more effective than HCTZ 25 mg in reducing blood pressure (-17.4/-12.2 versus -14.7/-10.3 mm Hg; p<0.001). Adverse event rates were similar with aliskiren versus HCTZ based therapy, 65.2% versus 61.5%, respectively. Hypokalemia was more frequent with HCTZ based therapy versus aliskiren based therapy, 17.9% versus 0.9%, respectively, p<0.0001.

Utilizing the study population mentioned above, a post hoc analysis of 396 obese patients (body mass index ≥ 30 kg/m^2) was performed.[231] Aliskiren monotherapy provided significantly greater BP reductions than HCTZ at week 12 (-16.7/-12.3 versus -12.2/-9.1 mm Hg, p≤ 0.001) in the subgroup of obese patients. At week 52, blood pressure reductions were also significantly greater with aliskiren-based therapy than HCTZ-based therapy (-19.9/-15.5 versus -17.5/-13.3 mm Hg; p=0.138 for SBP and p=0.007 for DBP). Mean BP reductions from baseline with aliskiren-based therapy were similar in obese and nonobese patients. However, HCTZ-based therapy provided significantly smaller mean reductions in BP from baseline in obese patients versus nonobese patients (p<0.05). Aliskiren-based therapy was generally well tolerated in obese patients and was associated with a significantly lower incidence of hypokalemia (one versus 14%, p<0.0001) than HCTZ-based therapy.

The efficacy, safety, and tolerability of a single-pill combination (SPC) of aliskiren/HCTZ were investigated in patients non-responsive to HCTZ 25 mg therapy.[232] Patients (n=722) with mean sitting diastolic BP ≥90 and <110 mm Hg despite four weeks of therapy with HCTZ 25 mg were randomized to eight weeks of once-daily, double-blinded treatment with a SPC of aliskiren/HCTZ 300/25 mg or 150/25 mg, or continued HCTZ 25 mg monotherapy. Least-squares mean changes in mean sitting systolic/diastolic BP (msSBP/DBP) from baseline were analyzed for the intention-to-treat population. Aliskiren/HCTZ 300/25 mg and 150/25 mg SPCs lowered msSBP/DBP from baseline significantly more than HCTZ alone (-16.7/-10.7 and -12.9/-8.5 mm Hg, respectively, compared to -7.1/-4.8 mm Hg; both p<0.001). Rates of BP control (<140/90 mm Hg) were also significantly higher with aliskiren/HCTZ 300/25 mg (58%) and 150/25 mg (49%) when compared with HCTZ (26%; both p<0.001). Additionally, results showed that aliskiren/HCTZ 300/25 mg provided significantly greater msSBP/DBP reductions and rates of BP control than the 150/25 mg SPC dose (all p<0.05). Aliskiren/HCTZ SPC treatment

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showed similar tolerability to HCTZ alone, and aliskiren/HCTZ showed a numerically lower incidence of hypokalemia (serum potassium <3.5 mmol/L; aliskiren/HCTZ, 1.3-2.2%: HCTZ alone, 3.4%).

In another study, efficacy, safety and tolerability of a single-pill combination (SPC) of aliskiren/HCTZ was investigated in patients non-responsive to aliskiren monotherapy.[233] Patients (n=880) with mean sitting diastolic BP (msDBP) >90 and ≤ 110 mm Hg despite four weeks of therapy with aliskiren 300 mg were randomized to eight weeks of once-daily, double-blind treatment with a SPC of aliskiren/HCTZ 300/25 mg or 300/12.5 mg, or continued aliskiren 300 mg monotherapy. Least-squares mean changes in mean sitting systolic/diastolic BP (msSBP/DBP) from baseline were analyzed for the intent-to-treat population. Aliskiren/HCTZ 300/25 mg and 300/12.5 mg lowered msSBP/DBP from baseline significantly more than aliskiren alone (-15.9/-11 mm Hg and -13.5/-10.5 mm Hg, respectively, compared to -8/-7.4 mm Hg; both p<0.001). Rates of BP control (<140/90 mm Hg) were also significantly higher with aliskiren/HCTZ 300/25 mg (60.2%) and 300/12.5 mg (57.9%) when compared to aliskiren 300 mg alone (40.9%; both p<0.001). Aliskiren/HCTZ SPC treatment showed similar tolerability to aliskiren monotherapy.

A randomized double-blind study included 688 patients with a mean sitting SBP ≥160 mm Hg and <180 mm Hg.[234] After a two- to four-week washout period, patients were randomized to once-daily aliskiren/hydrochlorothiazide (HCTZ) 150/12.5 mg or aliskiren 150 mg for one week and then the dose was doubled for an additional 11 weeks. At week 12, aliskiren/HCTZ lowered BP significantly more than aliskiren (least-squares mean between-treatment differences [95% CI] were -9.7 [-12 to -7.4] for SBP and -4.5 [-5.8 to -3.2] for DBP; both p<0.0001). Similar BP reductions were seen in the subgroups of patients with isolated systolic hypertension and obesity.

aliskiren (Tekturna) with valsartan (Diovan®)

A randomized, double-blind, placebo-controlled, parallel-group, four-arm, dose escalation study of 1,797 patients was conducted over eight weeks. Patients received aliskiren 150 or 300 mg or valsartan 160 or 320 mg either alone or in combination.[235] Inclusion criteria were baseline mean sitting DBP of 95 to 100 mm Hg and eight hour daytime ambulatory DBP greater than or equal to 90 mm Hg. Patients were randomized to once daily therapy with aliskiren 150 mg, valsartan 160 mg, a combination of aliskiren 150 mg and valsartan 160 mg, or placebo for four weeks. Forced titration to double the initial dose continued for an additional four weeks. Greater blood pressure reductions were achieved with combination therapy compared with monotherapy. Reduction in the mean sitting DBP compared to baseline was 12.2 mm Hg with combination therapy, 9 mm Hg with aliskiren 300 mg (p<0.0001), 9.7 mm Hg with valsartan 320 mg (p<0.0001) and 4.1 mm Hg with placebo (p<0.0001). Rates of adverse events were similar among all groups.

An eight-week, randomized, double-blind, placebo-controlled, multifactorial, parallel group, multicenter study of 1,123 hypertensive patients compared blood pressure lowering effects of aliskiren and valsartan monotherapy or in combination versus placebo.[236] Aliskiren monotherapy at doses of 75 mg to 300 mg resulted in similar blood pressure reductions as valsartan 80 mg to 320 mg. The combination of aliskiren and valsartan decreased blood pressure more than the individual monotherapies. All treatments were well tolerated.

Patients (n=465) with hypertension, increased ventricular wall thickness and body mass index >25 kg/m^2 were randomized to receive aliskiren 300 mg, losartan 100 mg or the combination of both for nine months.[237] Add-on therapy, with the exception of other inhibitors of the renin-angiotensin-

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aldosterone system and beta-blockers, was allowed to treat patients to standard blood pressure targets. Assessment of left ventricular (LV) mass at baseline and at study completion was performed using cardiovascular magnetic resonance imaging. The change in LV mass index from baseline to follow-up in the combination and losartan arms was the primary end point; the secondary objective was to determine whether aliskiren was noninferior to losartan in reducing LV mass index from baseline to follow-up. Systolic and diastolic blood pressure was reduced similarly in all groups (6.5+/-14.9/3.8+/-10.1 mm Hg in the aliskiren group; 5.5+/-15.6/3.7+/-10.7 mm Hg in the losartan group; 6.6+/-16.6/4.6+/-10.5 mm Hg in the combination arm; p<0.0001 within groups, p=0.81 between groups). LV mass index was reduced significantly from baseline in all treatment groups (4.9-, 4.8-, and 5.8 g/m^2 reductions in the aliskiren, losartan, and combination arms, respectively; p<0.0001 for all treatment groups. The reduction in LV mass index in the combination group was not significantly different from that with losartan alone (p=0.52). Aliskiren was as effective as losartan in reducing LV mass index (p<0.0001 for noninferiority). Safety and tolerability were similar across all treatment groups.

aliskiren (Tekturna) with lisinopril

An eight-week, randomized, double-blind, parallel group, multicenter study of 183 patients with severe hypertension compared aliskiren 150 mg to lisinopril 20 mg. Dose titration to aliskiren 300 mg or lisinopril 40 mg and subsequent addition of HCTZ occurred if additional blood pressure reduction was needed.[238] Aliskiren showed similar reductions to lisinopril in both SBP (aliskiren 20 mm Hg versus lisinopril 22.3 mm Hg, mean treatment difference 2.8 mm Hg, 95% CI, -1.7 to 7.4) and DBP (aliskiren 18.5 mm Hg versus lisinopril 20.1 mm Hg, mean treatment difference 1.7 mm Hg, 95% CI, -1 to 4.4). About 50% of both groups required the addition of HCTZ. The percentage of patients reporting adverse events was similar in the two groups.

aliskiren (Tekturna) with ramipril

An eight-week, randomized, double-blind, multicenter study of 837 patients with diabetes mellitus and hypertension compared aliskiren 150 mg titrated to 300 mg after four weeks, ramipril 5 mg titrated to 10 mg, or aliskiren/ramipril.[239] The combination reduced DBP more than aliskiren (p=0.043) or ramipril (p=0.004) monotherapy, resulting in an additional 4.6/2.1 mm Hg reduction. The aliskiren and ramipril combination also provided significantly greater mean reductions from baseline in SBP than ramipril (p<0.0001), but not aliskiren (p=0.088). Aliskiren monotherapy was statistically non-inferior to ramipril for DBP reduction (p=0.0002) and statistically superior for SBP reduction (p=0.021). Aliskiren significantly reduced plasma renin activity both as monotherapy (by 66%, p<0.0001) and combination therapy (by 48%, p<0.0001), despite large increases in plasma renin concentration in all groups. Aliskiren was well-tolerated.

A double-blind study compared aliskiren and ramipril alone and combined with HCTZ in patients with hypertension.[240] Following a two to four week placebo run-in period, 842 patients were randomized to aliskiren 150 mg or ramipril 5 mg. Dose titration (to aliskiren 300 mg/ramipril 10 mg) and subsequent HCTZ addition (12.5 mg, titrated to 25 mg if needed) were permitted at weeks six, 12, 18 and 21 for inadequate blood pressure control. Patients completing the 26-week active-controlled treatment period were re-randomized to their existing regimen or placebo for a four-week double-blind withdrawal phase. At week 26, the aliskiren group produced greater mean reductions in mean sitting systolic blood pressure (msSBP) (17.9 versus 15.2 mm Hg, p=0.0036) and mean sitting diastolic blood pressure (msDBP) (13.2 versus 12 mm Hg, p=0.025), and higher rates of SBP (<140 mm Hg; 72.5 versus

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64.1%, p=0.0075) compared with the ramipril group. During withdrawal, blood pressure increased more rapidly after stopping ramipril than aliskiren; median blood pressure reached 140/90 mm Hg after one and four weeks, respectively. Blood pressure reductions were maintained with continued active treatment. Adverse event rates were similar with aliskiren (61.3%) and ramipril (60.4%); cough was more frequent with ramipril (9.5%) compared with aliskiren (4.1%).

A 36-week, randomized, double-blind, parallel-group, active-controlled, optional-titration study was performed to compare efficacy and safety of aliskiren with ramipril for the treatment of essential systolic hypertension in 901 elderly (≥65 years of age) patients with SBP ≥140 mm Hg.[241] Aliskiren 150-300 mg per day (n=457) or ramipril 5-10 mg per day (n=444) was administered for 12 weeks. HCTZ 12.5-25 mg per day was added at week 12, and amlodipine 5-10 mg per day was added at week 22 if blood pressure control was not achieved. Non-inferiority of aliskiren versus ramipril monotherapy for change from baseline in mean sitting SBP (msSBP) at week 12 was the primary end point. Decreases from baseline msSBP and mean sitting diastolic BP with aliskiren monotherapy (-14 and -5.1 mm Hg, respectively) were non-inferior (p<0.001 for both values) and superior to ramipril monotherapy (-11.6, -3.6 mm Hg; p=0.02, p<0.01, respectively). More patients achieved BP control with aliskiren (42 %) than ramipril (33%; p<0.01). At week 36, fewer patients receiving aliskiren-based therapy required add-on treatment with HCTZ or amlodipine (p=0.01 and 0.048, respectively). More patients receiving ramipril reported cough (p<0.001).

aliskiren (Tekturna) with amlodipine

Aliskiren 150 mg and 300 mg and amlodipine besylate 5 mg and 10 mg were studied alone and in combination in 1,685 patients in a randomized, double-blind, placebo-controlled, multifactorial, eight-week, study.[242] Treatment with aliskiren and amlodipine resulted overall in significantly greater reductions in diastolic and systolic blood pressure compared to the respective monotherapy components.

aliskiren (Tekturna) with amlodipine or hydrochlorothiazide

A randomized, double-blind, placebo-controlled trial (APOLLO) assessed the BP lowering efficacy of aliskiren or placebo with amlodipine or hydrochlorothiazide in 1,759 elderly individuals with a systolic blood pressure between 130 and 159 mm Hg.[243] Following a five-week active run-in, participants were randomized to aliskiren 300 mg or placebo as well as an additional antihypertensive agent (hydrochlorothiazide 25 mg, amlodipine 5 mg) or placebo. The study was terminated early after 7.2 months. Three levels of BP reductions were achieved, adjusted mean BP reductions of 3.5/1.7 mm Hg (p<0.001) by aliskiren, 6.8/3.3 mm Hg (p<0.001) by hydrochlorothiazide or amlodipine, and 10.3/5 mm Hg (p<0.001) by double antihypertensive therapy compared with placebo. No statistically significant differences were found in number of cerebrovascular disease events based on increments of BP reduction (p for HR=not significant [NS]), but the overall number of events was limited (number of events = 25). Study drugs were well tolerated with few serious adverse events during all phases and with no significant differences between groups.

Meta-analyses

A meta-analysis of seven trials including 33,960 patients found that in stable CAD patients with preserved left ventricular function, ACE inhibitors were associated with reduced total and cardiovascular mortality, MI, and stroke.[244] Drugs included in the meta-analysis were enalapril, perindopril, quinapril, ramipril, and trandolapril. A network meta-analysis of ACE inhibitors (captopril,

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enalapril, lisinopril, ramipril, trandolapril) assessed their impact on various heart failure outcomes (29 studies).[245] No significant difference was found between agents in blood pressure, stroke volume, or ejection fraction. Lisinopril was associated with higher all-cause mortality compared to placebo (odds ratio [OR]; 65.9, 95% credible interval [CrI], 1.91 to 239.6) or ramipril (OR, 14.65; 95% CrI, 1.23 to 49.5). However, as this was a network meta-analysis and most included studies were of short duration, results should be interpreted cautiously.

A review of six trials of aliskiren involving over 5,000 patients with mild to moderate hypertension found aliskiren to be no more effective than ACE inhibitors, ARBs, or diuretics for lowering blood pressure.[246] As expected, a review of 19 trials (n=13,614) found that the addition of hydrochlorothiazide or amlodipine to aliskiren was more effective than aliskiren alone; however, aliskiren with amlodipine was found to be more effective than aliskiren with hydrochlorothiazide.[247]

SUMMARY

Data from numerous clinical trials suggest, when given in equipotent doses, all ACE inhibitors are effective in the treatment of hypertension. Pharmacokinetic and pharmacodynamic differences do not support an advantage of any one agent over another in the majority of patients with hypertension. Likewise, guidelines on hypertension do not recommend one specific agent over another.

The 2013 ACC/AHA HF Guidelines consider ACE inhibitors a standard of therapy for HF, as they have consistently demonstrated a significant reduction in mortality. The evidence suggests the benefit of ACE inhibitors in CHF is a class effect. ACE inhibitors should be given to all CHF patients who are at high risk for CHD regardless of the presence or absence of concomitant hypertension.

Beneficial effects of ACE inhibitors are demonstrated in diabetic and nondiabetic nephropathies beyond those expected from lowering blood pressure. In patients with type 1 diabetes and hypertension, ACE inhibitors delay the progression of nephropathy regardless of the degree of albuminuria. ACE inhibitors and angiotensin receptor blockers (ARBs) delay the progression of nephropathy and delay the increase in albuminuria in hypertensive type 2 diabetics with microalbuminuria.

In the setting of AMI, ACE inhibitors prevent ventricular remodeling, attenuate ventricular dilatation over time, and decrease the likelihood of CHF, recurrent MI, and death in patients with LVD, and early ACE inhibitor therapy is recommended.

All ACE inhibitors have similar incidence rates of adverse events. Cough and central nervous system effects (e.g., dizziness and headache) are the most prevalent. Captopril has a slightly higher incidence of rash, likely due to its sulfhydryl side chain.

Aliskiren (Tekturna) offers an alternative in the treatment of hypertension, but at this time, evidence does not support a clear advantage over ACEIs and ARBs. Based on the halted ALTITUDE study, aliskiren containing drugs are contraindicated in combination with an ACEI or ARB in diabetics. Significant drug interactions with aliskiren (Tekturna) include irbesartan (Avapro), atorvastatin (Lipitor), furosemide and ketoconazole. The clinical significance of aliskiren's (Tekturna) unique mechanism has not been demonstrated in reduction of morbidity and mortality.

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