Angiotensin Modulators: ACE Inhibitors and Direct Renin Inhibitors Review

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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®)	generic	X (Pediatrics age 6-16 yrs)	--	--	--
captopril (Capoten®)	generic	X	X	X (in pts with LVD)	• Diabetic Nephropathy in type 1 diabetics
enalapril (Vasotec®)	generic	X (Pediatrics age 1 month - 16 yrs)	X (or asymptomatic LVD)	--	--
fosinopril (Monopril®)	generic	X (Pediatrics age 6-16 yrs)	X	--	--
lisinopril (Prinivil®, Zestril®)	generic	X (Pediatric age 6-16 yrs)	X	X (in hemo-dynamically stable pts)	--
moexipril (Univasc®)	generic	X	--	--	--
perindopril (Aceon®)	Solvay	X	--	--	• In stable CAD, reduces risk of cardiovascular mortality and non-fatal MI
quinapril (Accupril®)	generic	X	X	--	--
ramipril (Altace®)	generic (capsules) Monarch (tablets)	X	X (post-MI)	--	• Reduction of risk of MI, stroke, and death from cardiovascular causes
trandolapril (Mavik®)	generic	X	--	X (in pts with CHF or asymptomatic LVD)	--
Direct Renin Inhibitor					
aliskiren (Tekturna®)	Novartis	X	--	--	--

Diuretic Combination Products

Several ACE inhibitors and the direct renin inhibitor are available in combination with a diuretic for treatment of hypertension. The combination results in additional blood pressure reduction with minimal changes in adverse effect profile.[1] The JNC-VII guidelines suggest most patients require two medications for adequate control of hypertension.[2]

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

Overview

Hypertension affects over 30 percent of adult Americans.[3] Hypertension is an independent risk factor for the development of cardiovascular disease. The more elevated the blood pressure, the higher the risk of myocardial infarction (MI), stroke, heart failure, and kidney disease. To reduce the risk of cardiovascular events, the current blood pressure goal is less than 140/90 mm Hg. For patients with chronic renal disease or diabetes, the current goal for blood pressure therapy is less than 130/80 mm Hg.[4,5,6] Attainment of blood pressure goals results in a reduced risk of cardiovascular events.[7] 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 cardiovascular benefit in patients with hypertension, not the specific agent used.[8,9,10,11]

Angiotensin Modulators include the angiotensin-converting enzyme (ACE) inhibitors, the direct 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 rennin inhibitor, aliskiren (Tekturna).

Angiotensin-converting enzyme (ACE) inhibitors are now readily accepted as first-line therapy for treatment of essential hypertension. According to the JNC-VII guidelines, compelling

indications for ACE inhibitors are: congestive heart failure (CHF), post-myocardial infarction (MI), high-risk cardiovascular disease, diabetes mellitus, chronic kidney disease, and recurrent stroke prevention.[12] 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.[13,14,15,16,17]

In the ALLHAT study, the primary endpoint of combined fatal CHD and nonfatal acute MI were similar amongst chlorthalidone, amlodipine, and lisinopril treatment arms. Amlodipine had higher risk of heart failure and hospitalization related to heart failure or fatal heart failure compared to chlorthalidone, among diabetics and non-diabetics (RR 1.42, 95% confidence interval (CI), 1.23-1.64). Compared with chlorthalidone, lisinopril demonstrated higher rates of combined cardiovascular disease outcomes (33 percent versus 30.9 percent, RR 1.10), stroke (6.3 versus 5.6 percent, RR 1.15), and heart failure (8.7 versus 7.7 percent, RR 1.19). Several analyses of ALLHAT have been performed. A recent ALLHAT post hoc analysis found that in patients with metabolic syndrome and particularly in black patients, the findings do not support preferring an ACE inhibitor, CCB or alpha blocker to a thiazide diuretic despite their more favorable metabolic profiles.[18] A subgroup analysis of ALLHAT showed that despite a less favorable metabolic profile, thiazide-like diuretic initial therapy for hypertension offers similar, and in some instances possibly superior, cardiovascular disease outcomes in older hypertensive adults with metabolic syndrome, as compared with treatment with ACE inhibitors and CCBs.[19] A reanalysis of the ALLHAT data showed the higher risk of heart failure with amlodipine and lisinopril versus chlorthalidone was greatest in the first year (RR 2.2, 95% CI, 1.68 to 2.98 and RR 2.08, 95% CI, 1.56 to 2.78, respectively), whereas the unadjusted risk of hospitalized or fatal heart failure remained higher for amlodipine versus chlorthalidone (RR 1.35, 95% CI, 1.21 to 1.50) and lisinopril (RR 1.23, 95% CI, 1.09 to 1.38).[20]

ACE inhibitors are a cornerstone in the treatment of CHF.[21] Benefits of ACE inhibitor therapy are seen in patients with both mild and severe disease and are independent of CHF etiology. The ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in heart failure.[22] The evidence suggests the benefit of ACE inhibitors in CHF is a class effect.[23] 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.[24] Unfortunately, underdosing and underutilization of the ACE inhibitors in CHF patients are well documented. As a result, full benefits of ACE inhibitor therapy are not realized.[25]

Beneficial effects of ACE inhibitors are demonstrated in diabetic and nondiabetic nephropathies beyond those expected from lowering blood pressure.[26] In type 1 diabetic patients with 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.[27]

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.[28] ACE inhibitors should be started and continued indefinitely in all patients recovering from ST-elevation myocardial infarction (STEMI) with left ventricular ejection fraction (LVEF) of 40 percent or less and for those with hypertension, diabetes, or chronic kidney disease unless otherwise contraindicated.[29] ACE inhibitors are also considered a reasonable option in patients who are at lower risk.[30] Patients with non-ST-elevation myocardial infarction (NSTEMI) with LVD (LVEF less than 0.40), hypertension and diabetes mellitus, unless contraindicated, should receive ACE inhibitors indefinitely.[31]

In AMI, ACE inhibitors reduce 30-day mortality when therapy is initiated within 36 hours of the acute event.[32] Four studies with 98,496 MI patients were analyzed together.. Trials using captopril and lisinopril showed approximately 30 percent mortality reduction if therapy is initiated within 24 hours of MI symptom onset.[33,34]

The Agency for Healthcare Research and Quality (AHRQ) has published a comparative effectiveness report for the ACEIs and ARBs.[35] The ACEIs and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension. For mortality and major cardiovascular events, there is insufficient evidence to determine if there are any different effects of ACEIs versus ARBs on these serious outcomes. ACEIs have been shown to have a greater risk of cough than ARBs and the direct renin inhibitor.[36,37,38,39]

A direct renin inhibitor, aliskiren (Tekturna), is a new agent for the treatment of hypertension.[40] One recent study has shown it to have an antiproteinuric effect when used in combination with losartan (Cozaar®) in hypertensive patients with diabetic nephropathy. At this time, morbidity and mortality data are lacking for aliskiren.

Pharmacology

ACE inhibitors affect the renin-angiotensin-aldosterone system. 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.[41] 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.[42]

Aliskiren is a direct renin inhibitor and 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).[43]

Pharmacokinetics

Drug	Absorption (%)	Half-Life (hr)	Metabolism	Elimination (%)
ACE Inhibitors				
benazepril (Lotensin)[44]	37	10-11	Yes - to active benazeprilat	Renal: 88 Biliary: 11-12
captopril (Capoten)[45]	60-75	2	Yes	Renal: 80 Hepatic: 20
enalapril (Vasotec)[46]	55-75	11	Yes - to active enalaprilat	Renal: 60-78 Hepatic: 33
fosinopril (Monopril)[47]	36	12	Yes - to active fosinoprilat	Renal: 44-50 Hepatic: 46-50
lisinopril (Prinivil, Zestril)[48, 49]	25 (varies between 6-60)	12	None	Renal: 100
moexipril (Univasc)[50]	13	2-9	Yes - to active moexiprilat	Renal: 13 Hepatic: 52
perindopril (Aceon)[51]	75	-	Yes - to active perindoprilat	Renal: 100
quinapril (Accupril)[52]	60	3	Yes - to active quinaprilat	Renal: 61 Hepatic: 37
ramipril (Altace)[53]	50-60	13-17	Yes - to active ramiprilat	Renal: 60 Hepatic: 40
trandolapril (Mavik)[54]	80	6-10	Yes - to active trandolaprilat	Renal: 33 Hepatic: 66
Direct Renin Inhibitor				
aliskiren (Tekturna)[55]	2.5	40	None	Renal: 25

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.

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

Differences between agents with regard to structure and tissue specificity have been identified, but clinical relevance of the differences is not clear.[56] 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 percent, respectively, when administered with a high fat meal. In clinical trials, aliskiren (Tekturna) was administered without regard to meals. Patients should take aliskiren (Tekturna) at the same time each day.

Contraindications/Warnings[57,58,59,60,61,62,63,64,65,66,67,68]

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 direct 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. Pregnancy is considered a contraindication for use of any angiotensin modulating agent.

Hypersensitivity to any component of the formulations for ACE inhibitors and direct 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.

Caution should be used or these agents should be avoided in patients with hyperkalemia. Caution should be exercised when using aliskiren in volume and/or salt-depleted patients on high doses of diuretics.

Drug Interactions[69,70,71,72,73,74,75,76,77,78,79,80]

ACE inhibitors interact with azathioprine (neutropenia), cyclosporine (nephrotoxicity), lithium (neutropenia), NSAIDs (nephrotoxicity), and potassium-sparing diuretics, trimethoprim, or eplerenone (hyperkalemia). Concurrent use of loop and thiazide diuretics can increase the risk of hypovolemia, increasing the risk of nephrotoxicity.

Aliskiren (Tekturna) is metabolized by CYP3A4. Drug interactions have occurred with irbesartan (Avapro®) (50 percent reduction in aliskiren concentrations), atorvastatin (Lipitor®) (50 percent increase in aliskiren's maximum concentration and area under the curve), ketoconazole (80 percent 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 percent and 30 percent, respectively). Concomitant use of aliskiren with cyclosporine is not recommended. The effects of aliskiren 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, and amlodipine.

Adverse Effects

Hypertensive Patients

Drug	Headache	Dizziness	Fatigue	Cough	Rash	Angioedema
ACE Inhibitors						
benazepril (Lotensin)[81] n=964	6.2 (4.2)	3.6 (2.4)	2.4 (2.2)	1.2 (1)	reported	0.5
captopril (Capoten)[82]	0.5-2	0.5-2	0.5-2	0.5-2	4-7	0.001
enalapril (Vasotec)[83] n=2,314	3 (2.6)	4.3 (4.3)	1.1 (0.9)	2.2 (0)	1.4 (0.4)	0.2
fosinopril (Monopril)[84] n=688	> 1 (> 1)	1.6 (0)	> 1 (> 1)	2.2 (0)	0.2-1 (reported)	0.2-1
lisinopril (Prinivil, Zestril)[85,86] 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)[87] n=674	> 1 (> 1)	4.3 (2.2)	2.4 (1.8)	6.1 (2.2)	1.6 (0.9)	< 0.5
perindopril (Aceon)[88] n=789	23.8	8.2 (8.5)	7.9	12 (4.5)	2.3	0.1
quinapril (Accupril)[89] n=1,563	5.6 (10.9)	3.9 (2.6)	2.6 (1)	2 (0)	1.4 (1)	0.1
ramipril (Altace)[90] n=651	5.4	2.2	2 (1)	12	reported	0.3
trandolapril (Mavik)[91] n=832	> 1 (> 1)	1.3 (0.4)	> 1 (> 1)	1.9 (0.4)	0.3-1	0.13
Direct Renin Inhibitor						
aliskiren (Tekturna)[92]	> 1 (>1)	> 1 (>1)	> 1 (>1)	1.1* (0.6)	1 (0.3)	0.06-0.4

Adverse effects are reported as a percentage. Adverse effects data obtained are from the prescribing information and are not meant to be comparative. 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 percent.

Special Populations[93,94,95,96,97,98,99,100,101,102,103]

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.[104]

Aliskiren (Tekturna) has not been studied in patients less than 18 years of age.[105]

Pregnancy

ACE inhibitors and aliskiren (Tekturna) are contraindicated in second and third trimesters of pregnancy; they are in Pregnancy Category C for the first trimester and class D in the second and third trimesters.[106,107,108] ACE inhibitors and aliskiren (Tekturna) can cause severe fetal injury or fetal death during the second and third trimesters.

Other populations

Black patients receiving ACE inhibitor monotherapy have reported a higher incidence of angioedema compared to non-blacks. In controlled clinical trials, ACE inhibitors have less effect on blood pressure in black patients than in non-blacks.[109,110,111]

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)	10-40 mg daily	0.2 – 0.6 mg/kg/day; doses greater than 0.6 mg/kg or > 40 mg have not been studied	--	--	--	--	--	5, 10, 20, 40 mg tablets
captopril (Capoten)	25-150 mg three times daily	--	6.25-100 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)	5-40 mg daily	0.08 mg/kg/day up to 5 mg; doses greater than 0.58 mg/kg or > 40 mg have not been studied	2.5-20 mg twice daily	--	--	--	--	2.5, 5, 10, 20 mg tablets
fosinopril (Monopril)	10-40 mg daily	0.1-0.6 mg/kg/day; for children > 50 kg, 5 – 10 mg daily	10-40 mg daily	--	--	--	--	10, 20, 40 mg tablets
lisinopril (Prinivil/ Zestril)	10-40 mg daily	0.07 mg/kg/day up to 5 mg; doses greater than 0.61mg/kg or > 40 mg have not been studied	5-40 mg daily	5-10 mg daily	--	--	--	generic availability: 2.5, 5, 10, 20, 30, 40 mg tablets
moexipril (Univasc)	7.5-30 mg daily	--	--	--	--	--	--	7.5, 15 mg tablets
perindopril (Aceon)	4-16 mg daily	--	--	--	--	--	4 – 8 mg daily	2, 4, 8 mg tablets
quinapril (Accupril)	10-80 mg daily	--	5-20 mg twice daily	--	--	--	--	5, 10, 20, 40 mg tablets
ramipril (Altace)	2.5-20 mg daily	--	2.5-5 mg twice daily	--	--	2.5-10 mg daily	--	1.25, 2.5, 5, 10 mg generic capsules and brand tablets
trandolapril (Mavik)	1-4 mg daily	--	--	1-4 mg daily	--	--	--	1, 2, 4 mg tablets
Direct Renin Inhibitor								
aliskiren (Tekturna)	150-300 mg daily	--	--	--	--	--	--	150, 300 mg tablets

Combinations with Hydrochlorothiazide (HCTZ)

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

In patients with severe renal impairment (creatinine clearance is < 30 mL/min, serum creatinine exceeding 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 (generic only), 10/25 mg/mg tablets
fosinopril/HCTZ (Monopril-HCT)	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
Direct 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.[112]

captopril (Capoten) – Initial dose should be reduced for patients with significant renal impairment.[113]

enalapril (Vasotec) - 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.[114]

fosinopril (Monopril) – No dosage adjustments for fosinopril are necessary for renal impairment.[115]

lisinopril (Prinivil, Zestril) – For patients with renal impairment (serum creatinine exceeding 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.[116,117]

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.[118]

perindopril (Aceon) – In patients with renal impairment (creatinine clearance < 30 mL/min), safety and efficacy of perindopril have not been established.[119,120]

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.[121]

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 (Altace) 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 (Altace) 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.[122]

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.[123]

Direct Renin Inhibitor

aliskiren (Tekturna) – Aliskiren (Tekturna) 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.[124] 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 (Tekturna) with regard to meals. High fat meals decrease absorption substantially.[125]

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 percent 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.

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 between the ACE inhibitors in antihypertensive efficacy when equipotent doses of each agent are used.[126]

Leonetti and colleagues reviewed ACE inhibitors to determine which agent should be used for specific patients.[127] The authors found no significant difference in antihypertensive efficacy or adverse effect profiles between 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.[128] 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.[129] The authors concluded the overall mortality results were consistent with those of two major trials, SOLVD and CONSENSUS.[130] An extension of the SOLVD trial demonstrated enalapril used for three to four years extended median survival by 9.4 months.[131]

Numerous studies cite underutilization of ACE inhibitors in the treatment of CHF and acute MI.[132,133,134,135] 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 percent lower risk of death or hospitalization for any reason (p=0.002) and 24 percent fewer hospitalizations for heart failure (p=0.002) compared to the low dose group.[136] In patients with severe heart failure, the use of high-dose lisinopril, beta-blocker, and digoxin therapy had 12 percent lower risk of death and hospitalization over one year than patients who received low-dose lisinopril only (p=0.006).[137]

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.[138] Captopril and losartan improved systolic and overall LVD function, but greater benefit was observed with captopril.[139]

Ramipril (Altace) reduced mortality in patients with heart failure following acute MI.[140] In patients with LVD after acute MI, trandolapril therapy decreased mortality, 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.[141,142]

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.[143] Ramipril reduced the rate of development of new onset heart failure by 24 percent in high-risk patients with ejection fractions >0.40 (preserved left ventricular function).[144] 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.[145] In another study, low-dose ramipril 1.25 mg daily had no effect on cardiovascular and renal outcomes of patients with type 2 diabetes and albuminuria, despite a slight decrease in blood pressure and urinary albumin concentration.[146]

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.[147] The primary outcome was 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 percent) group did not differ from placebo (19.5 percent) 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, 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=0.40; 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.[148] 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.[149] Monotherapy with perindopril (Aceon) 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 percent for the composite of cardiovascular mortality, MI, or cardiac arrest over the mean study period of more than four years.[150] 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.[151] Over a median of 4.3 years, the composite outcome was reported in 12.6 versus 15.5 percent for perindopril and placebo groups, respectively (relative risk reduction, 19 percent [(95 percent CI, -7 to 38 percent), 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.[152] In the double-blind, randomized trial, 1,252 patients aged 65 years or older with a LVEF of 40 percent or higher and a recent history of MI were enrolled. The primary endpoint reached statistical significance and occurred in 35 percent and 57 percent of the perindopril (Aceon) and placebo groups, respectively (absolute risk reduction 0.22; 95% CI, 0.16 to 0.28; p<0.001). Fewer patients on perindopril (Aceon) experienced remodeling defined as ≥ eight percent increase in LV end diastolic volume as measured by echocardiography (28 versus 51 percent 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 CAD patients with normal or slightly reduced left ventricular function were randomized to trandolapril 4 mg daily or placebo in addition to intensive conventional therapy.[153] Patients (mean age 64 years) had a mean blood pressure of 133/78 mm Hg and mean left ventricular ejection fraction (LVEF) of 58 percent at baseline. Of those who received intensive therapy, 72 percent had a history of coronary revascularization, and 70 percent 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 percent 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.[154] 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.[155] Newly diagnosed diabetes was less frequent in the verapamil SR group versus atenolol group (7.0 percent versus 8.2 percent, 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. Addition of trandolapril to verapamil SR decreased risk of new-onset diabetes and addition of hydrochlorothiazide to atenolol increased the risk.

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.[156] 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 percent versus 16.7 percent, RR, 1.01, 95% CI, 0.94 to 1.09), in the ramipril versus telmisartan groups, respectively. Telmisartan group had lower rates of cough (1.1 percent versus 4.2 percent, p<0.001) and angioedema (0.1 percent versus 0.3 percent, p=0.01) and a higher rate of hypotensive symptoms (2.6 percent versus 1.7 percent, p<0.001) compared to ramipril. The rate of syncope was the same in both groups (0.2 percent). In the combination group, the primary outcome occurred in 1,386 patients (16.3 percent, RR 0.99, 95% CI, 0.92 to 1.07) and there was an increased risk of hypotensive symptoms (4.8 percent versus 1.7 percent, p<0.001), syncope (0.3 percent versus 0.2 percent, p=0.03), and renal dysfunction (13.5 percent versus 10.2 percent, 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.

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 percent versus 13.5, respectively (HR 1.00, 95% CI, 0.92 to 1.09) but was increased with combination therapy 14.5 percent (HR 1.09, 95% CI, 1.01 to 1.18, p=0.037).**[157]** 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.

Direct 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 (Tekturna) 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.[158] Greater blood pressure reductions were achieved with combination therapy compared with monotherapy.

Aliskiren (Tekturna) was studied in obese patients (body mass index ≥ 30 g/m^2) with hypertension.[159] 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 percent of patients.

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 (Tekturna) 150 or 300 mg or valsartan (Diovan) 160 or 320 mg either alone or in combination.[160] Inclusion criteria were baseline mean sitting DBP of 95 to 100 mg 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 with valsartan 320 mg (p<0.0001) and 4.1 mm Hg with placebo (p<0.0001). Rates of adverse events were similar between 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 (Tekturna) and valsartan (Diovan) monotherapy or in combination versus placebo.[161] Aliskiren (Tekturna) monotherapy at doses of 75 mg to 300 mg resulted in similar blood pressure reductions as valsartan (Diovan) 80 mg to 320 mg. The combination of aliskiren (Tekturna) and valsartan (Diovan) decreased blood pressure more than the individual monotherapies. All treatments were well tolerated.

aliskiren (Tekturna) with losartan (Cozaar)

AVOID was a randomized, double-blind, multicenter, study of 599 patients with hypertension and type 2 diabetic nephropathy which evaluated the renoprotective effects of aliskiren.[162] There was a three month, open-label run-in period where patients received 100 mg losartan daily. Then patients were randomized to six months of aliskiren (150 mg daily for three months followed by three months of 300 mg daily) or placebo in addition to losartan. Treatment with 300 mg of aliskiren daily, as compared with placebo, reduced the primary outcome of mean urinary albumin-to-creatinine ratio by 20 percent (95% CI, 9 to 30; p<0.001), with a reduction of 50 percent or more in 24.7 percent of the patients who received aliskiren as compared with 12.5 percent of those who received placebo (p<0.001). Blood pressure in the aliskiren group was slightly lower by the end of the study period (SBP, 2 mm Hg lower [p=0.07] and DBP, 1 mm Hg lower [p=0.08]. The total numbers of adverse and serious adverse events were similar in the 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 with dose titration to aliskiren 300 mg or lisinopril 40 mg and subsequent addition of HCTZ, if additional blood pressure reduction was needed.[163] Aliskiren showed similar reductions to lisinopril in both SBP (aliskiren 20.0 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, -1.0 to 4.4). About 50 percent 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.[164] 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 percent, p<0.0001) and combination therapy (by 48 percent, 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.[165] 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 mmHg, p=0.0036) and mean sitting diastolic blood pressure (msDBP) (13.2 versus 12.0 mmHg, p=0.025), and higher rates of SBP (<140 mmHg; 72.5 versus 64.1 percent, 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 mmHg after one and four weeks, respectively. Blood pressure reductions were maintained with continued active treatment. Adverse event rates were similar with aliskiren (61.3 percent) and ramipril (60.4 percent); cough was more frequent with ramipril (9.5 percent) compared with aliskiren (4.1 percent).

Meta-analysis

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.[166] Drugs included in the meta-analysis were enalapril, perindopril, quinapril, ramipril, and trandolapril.

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.[167]

A meta-analysis of nine trials evaluated the safety and tolerability of combination ACE inhibitor and ARB versus ACE inhibitor in patients with HF or LVD.[168] A total of 9,199 patients received combination therapy, and 8,961 patients received an ACEI only. Patients receiving combination therapy had an increased risk of developing any adverse effect by 2.3 percent (RR 1.27, 95% CI, 1.15 to 1.40, p<0.00001, inter-study heterogeneity or I^2 15.9 percent, number needed to harm [NNH]=42), hypotension by 1.1 percent (RR 1.91, 95% CI, 1.37 to 2.66, p=0.0002, I^2 26.6 percent, NNH=89), worsening renal function by 1 percent (RR 2.12, 95% CI, 1.30 to 3.46, p=0.003, I^2 67.3 percent, NNH=100), and hyperkalemia by 0.6 percent (RR 4.17, 95% CI, 2.31 to 7.53, p<0.00001, I^2 0 percent, NNH=149). There was no difference in angioedema (RR 0.88, 95% CI, 0.43 to 1.80, p=0.72, I^2 0 percent) or cough (RR 0.84, 95% CI, 0.65 to 1.09, p=0.19, I^2 = 0 percent). This meta-analysis found the combination of ACE inhibitor and ARB combination therapy to be associated with increased adverse events in patients with LVD compared to ACE inhibitor therapy.

A meta-analysis of six randomized comparative trials including 49,924 patients showed no significant differences between ARB and ACEI on the risk of MI (OR 1.01, 95% CI, 0.95 to 1.07, p=0.75), CV mortality (OR 1.0, 95% CI, 0.98 to 1.08, p=0.23) and total mortality (OR 1.03, 95% CI, 0.97 to 1.10, p=0.20).[169] Overall, the risk of stroke was slightly lower with ARBs than ACEI (OR 0.92, 95% CI, 0.85 to 0.99; p=0.037), the direct ACEIs and ARBs comparison showing a non significant trend in a similar direction. Statistical heterogeneity among trials was not significant, with a low to null inconsistency statistic, for stroke (p=0.67), MI (p=0.86), CV mortality (p=0.14) and total mortality (p=0.12).

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.

ACE inhibitors are 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 type 1 diabetic patients with 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 sulphydryl 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. Significant drug interactions with aliskiren (Tekturna) include irbesartan (Avapro), atorvastatin (Lipitor), furosemide and ketoconazole. Recent data has shown a potential diabetic renoprotective effect for aliskiren (Tekturna) in combination with an ARB. The clinical significance of aliskiren's (Tekturna) unique mechanism has not been demonstrated in reduction of morbidity and mortality.

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